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ROLE OF INFECTION AND INFLAMMATION IN ACUTE CORONARY SYNDROME

By

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Dissertation submitted to the

Tamil Nadu Dr.M.G.R Medical university, Chennai

In partial fulfilment of the requirements for the degree of

Doctor of Medicine in General Medicine

Under the Guidance of

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This is to certify that the dissertation entitled, **"ROLE OF INFECTION AND INFLAMMATION IN ACUTE CORONARY SYNDROME**" is the bonafide original work of **Dr.ArchanaRatnaPotluri** in partial fulfilment of the requirements for the degree of Doctor of Medicine in General Medicine

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This is to certify that the dissertation entitled, **"SERUM MAGNESIUM AS AN EFFECTIVE TOOL IN MONITORING THE CONTROL OF TYPE II DIABETES MELLITUS**" is the bonafide original research work of **Dr. ArchanaRatnaPolturi**under the guidance of **Dr.K.JayachandranM.D**, HOD & Professor,Department of General Medicine &**Dr.G.Rajendiran MD,DM,** HOD & Professor,Department of Cardiology, P.S.G IMSR, Coimbatore **i**n partial fulfilment of the requirements for the degree of Doctor of Medicine in General Medicine.

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I hereby declare that this dissertation entitled **"ROLE OF INFECTION AND INFLAMMATION IN ACUTE CORONARY SYNDROME"** is a bonafide and genuine research work carried out by me under the guidance of**Dr .K. Jayachandran M.D**, HOD & Professor, Department of General Medicine &**Dr .G. Rajendiran MD,DM,** HOD & Professor, Department of Cardiology, P.S.G IMSR, Coimbatore.

This dissertation is submitted to the Tamil Nadu Dr. M.G.R Medical University in fulfilment of the University regulations for the award of MD degree in General Medicine. This dissertation has not been submitted for award of any other degree or diploma.

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TABLE OF CONTENTS

GLOSSARY

ACS – acute coronary syndrome

AWMI – anterior wall myocardial infarction

AW+LWMI – anterior wall and lateral wall myocardial infarction

CAD- coronary artery disease

CAG – coronary angiogram

ECG- electrocardiogram

HTN- hypertension

HSP- heat shock protein

HSP 60 heat shock protein 60

hsCRP – high sensitivity C reactive protein

IWMI – inferior wall myocardial infarction

IWMI +PWMI – inferior and posterior wall myocardial infarction

MI – myocardial infarction

PCI – percutaneous coronary intervention

PWMI – posterior wall myocardial infarction

RDA – recommended dietary allowance

STEMI – st elevation myocardial infarction

T2DM – type 2 diabetes mellitus

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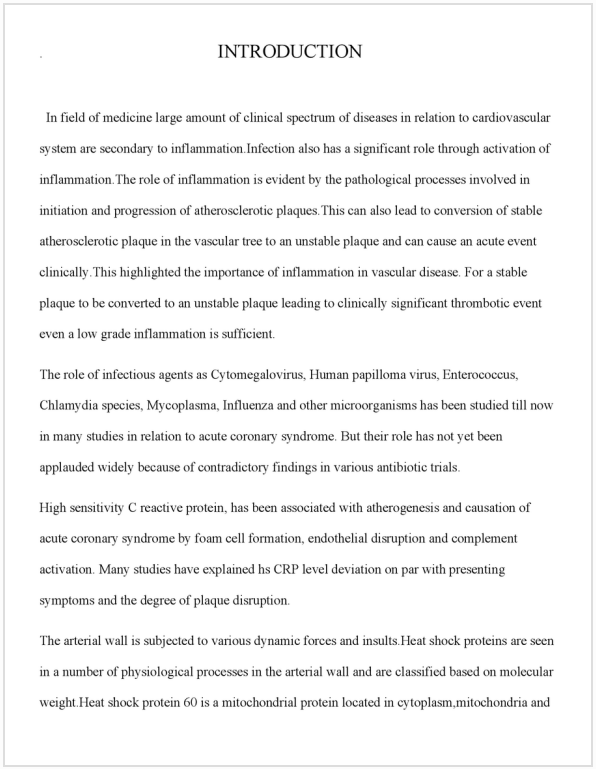

INTRODUCTION

In field of medicine large amount of clinical spectrum of diseases in relation to cardiovascular system are secondary to inflammation.Infection also has a significant role through activation of inflammation.The role of inflammation is evident by the pathological processes involved in initiation and progression of atherosclerotic plaques.This can also lead to conversion of stable atherosclerotic plaque in the vascular tree to an unstable plaque and can cause an acute event clinically.This highlighted the importance of inflammation in vascular disease. For a stable plaque to be converted to an unstable plaque leading to clinically significant thrombotic event even a low grade inflammation is sufficient.

The role of infectious agents as Cytomegalovirus, Human papilloma virus, Enterococcus, Chlamydia species, Mycoplasma, Influenza and other microorganisms has been studied till now in many studies in relation to acute coronary syndrome. But their role has not yet been applauded widely because of contradictory findings in various antibiotic trials.

High sensitivity C reactive protein, has been associated with atherogenesis and causation of acute coronary syndrome by foam cell formation, endothelial disruption and complement activation. Many studies have explained hs CRP level deviation on par with presenting symptoms and the degree of plaque disruption.

The arterial wall is subjected to various dynamic forces and insults.Heat shock proteins are seen in a number of physiological processes in the arterial wall and are classified based on molecular weight.Heat shock protein 60 is a mitochondrial protein located in cytoplasm,mitochondria and

TITLE : ROLE OF INFECTION AND INFLAMMATION IN ACUTE CORONARY SYNDROME

BACKGROUND :

The relation of infection with acute coronary syndrome is ever contradictory.Many antibiotic trials have failed in treating acute coronary syndrome.We have planned to focus on the concept of molecular mimicry between infectious agents and human proteins leading to inflammation and thus clinical syndromes of atherosclerosis secondary to these inflammatory reactions mounted against human antigens.One such preserved hyman chaperone is HSP 60 from prokaryotic age which shares molecular mimicry with many viral and bacterial human shock proteins.When inflammation is mounted against these HSP,the released inflammatory cascade molecules cause atherosclerosis and/or plaque destabilization and acute coronary syndrome.

AIM:

To study the role of infection in activating inflammatory pathwasy in the pathogenesis of atherosclerosis and acute coronary syndrome

OBEJECTIVE:

T o evaluate the role of bacterial and viral infection as a risk factor for STEMI through analysis of circulating levels of heat shock protein 60 in ACS patients on comparision with controls without ACS

To measure level of inflammation with high sensitivity c reactive eprotein and to evaluate its relation with HSP 60 and traditional risk factors of ACS.

METHODOLOGY AND RESULTS :

Ours is a case control study with 333 STEMI cases and 27 controls without ACS are studied.Traditional risk factors for ACS are assessed in both groups along with measurement of HSP 60 and hsCRP . HSP 60 and hsCP are considered to be indirect markers for infection and inflammation respectively.HSP60 is measured through spectrometric method analyzed through ELISA while hsCRP is read through automated COBAS analyzer. In cases further evaluation of features of echocardiography and coronary angiogram are studied.We found that circulating levels of hsCRP has statistical significance in cases($p<0.05$) while levels of HSP 60 donot have significant p value but have ODDS ratio of 1.54 indicating the possibility of relation of infection with incidence of acute coronary syndrome and its outcome.On regression analysis of all traditional risk factors for ACS they donot seem to influence the levels of hsCRP and HSP 60 in cases and controls in a statistically significant manner.

INTRODUCTION

In field of medicine large amount of clinical spectrum of diseases in relation to cardiovascular system are secondary to inflammation. Infection also has a significant role through activation of inflammation. The role of inflammation is evident by the pathological processes involved in initiation and progression of atherosclerotic plaques. This can also lead to conversion of stable atherosclerotic plaque in the vascular tree to an unstable plaque and can cause an acute event clinically. This highlighted the importance of inflammation in vascular disease. For a stable plaque to be converted to an unstable plaque leading to clinically significant thrombotic event even a low grade inflammation is sufficient.

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The arterial wall is subjected to various dynamic forces and insults. Heat shock proteins are seen in a number of physiological processes in the arterial wall and are classified based on molecular weight. Heat shock protein 60 is a mitochondrial protein located in cytoplasm, mitochondria and plasma. Under conditions of stress, this molecule comes out and mediates apoptosis via immune mechanism activation and antibody

production. By molecular mimicry mechanism ,when infection occurs, production of antibodies against these infectious agents act on heat shock proteins too which can be simultaneously released during disease associated stress conditions or hemodynamic alterations. This causes plaque instability leading to acute coronary syndrome. Many viruses, bacterial infection(Chlamydia, Helicobacter pylori) mount a autoimmune response in blood vessel and establish role of infection in inflammatory cascades involved in atherosclerosis.

However, role in acute coronary syndrome has to be established in developing countries like India where rate of infection is rampant. In our study, we intend to evaluate the role of infection through measuring HSP 60 level in plasma causing activation of inflammation(through measuring hs CRP) and leading to acute coronary syndrome independent of traditional risk factors.

TITLE OF THE STUDY:

Role of infection and inflammation in acute coronary syndrome.

AIM OF THE STUDY:

To study about the role of infection in activating inflammatory pathways in the pathogenesis of atherosclerosis and acute coronary syndrome.

Primary Objectives:

- To evaluate the role of bacterial and viral infection as a risk factor for STEMI through analysis of circulating levels of heat shock protein 60 in Acute Coronary Syndrome patients in comparison with subjects without Acute Coronary Syndrome in 20 to 80 years age group
- To measure the level of circulating inflammatory marker, high sensitivity C reactive protein and to analyze its levels on comparision with HSP 60 levels, to evaluate the relation between infection and inflammation leading to plaque disruption and Acute Coronary Syndrome

Secondary Objectives:

- To correlate the inflammatory markers levels with the coronary angiogram, Echocardiographic and electrocardiogram findings in subjects with Acute Coronary Syndrome
- To study the relation & independent risk evaluation of the traditional risk factors in comparison with markers of inflammation and infection(HSP-60,hsCRP) in cases and controls

National Significance with Rationale:

India being a developing country ,has increasing incidence of infectious disease burden and acute coronary syndrome .Cardiovascular diseases are leading cause of mortality in our nation.

The analysis of role of infections in ACS through inflammatory pathways has to be evaluated in Indian population.

Our study will be the first study to evaluate both viral & bacterial infections role in ACS in relation to inflammation in South India.

JUSTIFICATION:

The role of inflammation in acute coronary syndrome has been proven. However the role of infection in acute coronary syndrome has not yet been proven and the earlier antibiotic trials in acute coronary syndrome patient have failed. Here is a trial to justify the role of infection in relation to inflammation in acute coronary syndrome patients which can explain the reason for the failure of antibiotic trial and explain the molecular mimicry mechanism of infection leading to acute coronary syndrome.

OUTCOME MEASURES:

Role of infection in acute coronary syndrome through evaluation of circulating levels of heat shock protein-60 Evaluating relation between traditional risk factors and infection and inflammatory markers Measure the differences in values of these markers among cases and controls Coronary angiogram, echocardiographic and electrocardiogram findings relation with these circulating infectious and inflammatory markers

REVIEW OF LITERATURE

1. Acute Coronary Syndrome(ACS):

Acute coronary syndrome is a unifying term representing a common end result ,acute myocardial ischemia. It encompasses acute MI (resulting in ST segment elevation or non ST segment elevation electrocardiographically) and unstable angina.1.This definition is important clinically in deciding the treatment option for the patient.2.

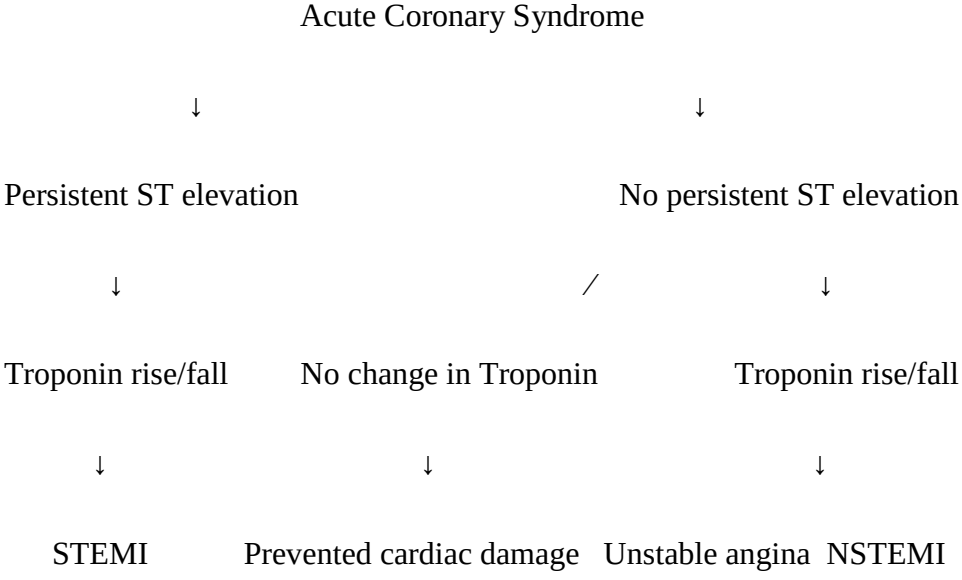
2.Clinical Presentation:

Acute ischemic pain ,lasting for over 20 minutes ,associated with inadequate supply of blood to heart muscle due to plaque rupture, fissuring, erosion or a combination with superimposed intracoronary thrombus is 80% of times presenting clinical features in ACS.1,2. Unlike stable angina even minimal exercise or even at rest ischemia can occur. The pain may be intermittent and accompanied by diaphoresis, nausea, abdominal pain, syncope and dyspnea.3.Uncommon symptoms may include epigastric pain, indigestion, stabbing chest pain and they are more varied in diabetes, women, heart failure patients. As per Thygesen et al, universal definition of MI based on causative agent, five different types of MI have been classified.4.This classification is based on symptoms, electrocardiographic changes or cardiac biomarker elevation.

3. Clinical Classification of Different Types of Myocardial Infarction:

TYPE	DEFINITION	POSSIBLE CAUSATIVE AGENT
I	Spontaneous infarction due To dissection Plaque rupture, erosion, fissuring and	Primary coronary event
II	Secondary infarction due to ischemic imbalance	Endothelial dysfunction, coronary spasm, embolism, anemia, arrhythmias, respiratory failure, hypertension, hypotension
III	Cardiac Death	
IVa	PCI	
IVb	Stent thrombosis	
V	CABG	

Classical classification of ACS as adapted from Hawn et al and Nikus et al as follows,



As per Valentin Fuster et al, the term ACS first appeared in 1986 on a simple Pub Med search in an article describing the flow characteristics of coronary balloon catheters.6.As time evolved in 1992 ACS term included MI, unstable angina and ischemic sudden death.6.All these are part of spectrum of manifestations of the same atherosclerotic coronary artery substrate. These definitions have now evolved into a definition as described above as per 2012 iteration of the universal definition, which gives importance to the measurement of Troponin I or T.As reflected by both GRACE(Global Registry of Acute Coronary Events) and TIMI (Thrombolysis in Myocardial Infarction),biomarker negative patient are generally at lower risk for adverse events.7,8.Hence,we are planning to include STEMI patients as the case population in this study.

4. Pathogenesis of Acute Coronary Syndrome:

As per Filippo Crea and Giovanna Liuezzo, pathologically ACS can be classified into, 9

- Patients who have obstructive atherosclerosis and systemic inflammation
- Patients who have obstructive atherosclerosis without systemic inflammation
- Patients without obstructive atherosclerosis

This is important in view of varied clinical presentation of ACS as described above. Additionally a popularly being thought not always ACS is associated with activation of inflammation as evident by the observation that about 40% of the patients with ACS have low or very low levels of hs-CRP(high sensitivity C reactive protein),a very sensitive marker of inflammation.

Hence we are interested in evaluating the role of inflammation in our study in ACS(STEMI) patients. Our study is also intended to highlight the concept of ACS with obstructive atherosclerosis without systemic inflammation by evaluation of physical, emotional and possible environmental stressors which would be responsible for ACS by evaluation of these risk factors in our cases. The concept of obstructive lesions with systemic inflammation occurs by activation of innate and adaptive immunity.9.In our study we are focusing on the concept of chronic infection acitng as antigenic stimulation and activating the adaptive and later innate immunity through disease associated molecular pattern(DAMPS) activation of T cells in ACS.

5. STEMI Definition:

As per third universal definition of MI,STEMI is majorly defined based on electrocardiographic findings[4]. It is described as new ST elevation at the J point in two contiguous leads with the cut points ≥0.1 mV in all leads other than leads V2-V3,where

the following cut points apply:≥0.2mV in men ≥40 years & ≥0.25mV in men < 40 years or ≥ 0.15 mV in women.

The ECG pit falls leading to false positives can be(which are exclusion criteria in our study)

- Early repolarisation
- LBBB
- Pre excitation
- J point elevation syndrome e.g. Brugada syndrome
- Pericarditis/Myocarditis
- Pulmonary embolism
- Sub arachnoid hemorrhage
- Metabolic disturbances such as hyperkalemia
- Cardiomyopathy
- Lead transposition
- Cholecystitis
- Persistent juvenile pattern
- Malposition of precordial ECG electrodes
- Tricyclic antidepressants and phenothiazine intake

The causes of false negatives like,

- Prior MI with Q waves and or persistent ST elevation
- Right ventricular pacing
- LBBB

Are all considered as exclusion criteria in our study.

6. Global Burden of ACS:

Ischemic heart disease ranks in first place as the cause of mortality and for the loss of disability adjusted life years(DALYS) world wide, accounting for 7 million deaths and 129 million DALYS annually.[14] A significant loss in economy occurs due to cardiovascular disease accounting to 1/3rd of $47 trillion of total loss in economy due to non communicable disease for the coming 20 years.[14].Nearly 2/3rd of all IHDS,DALYS and more than half of deaths occur in low and middle income countries. Witnessing the epidemiological transition from the age of pestilence and famine , to age of receding pandemics to age of degenerative and man made disease, to age of delayed degenerative disease and to the on going age of obesity and inactivity helps us to explain the rise in the risk factors leading to IHD especially in low and middle income countries.

Rapid urbanization, mechanization of transport and increasingly sedentary jobs in low and middle income groups have led to an acceleration and overlap between the stages of epidemiological transition. Ever since 1990, the number of deaths and DALYS attributable to IHD have risen.[15]

This acceleration in the rise of NCDS without a decline in the infectious disease burden, has led to a challenging double burden of disease in many countries, especially in developing nations [14]. Through our study we want to analyze the relation between the infectious disease and cardiovascular disease.

7. National and Local Burden of ACS:

In India ,cardiovascular disease is an important cause of mortality and morbidity. Data from the Registrar General of India reported greater age adjusted cardiovascular mortality in southern and eastern states of the country[17]. Coronary heart disease mortality is higher in urban population than in rural population as per Rajeev Gupta et al study [17]. It

has been reported that there were significant regional variations ,with high CVD mortality in Goa, Tamil nadu, Andhra Pradesh and Punjab and low mortality in central states of Uttar Pradesh,Madhya Pradesh and Rajasthan. As per Shraddha Chauhan and Dr.Bani Tamber Aeri, CVD in India ranks first among top 5 causes of deaths in Indian population and the future trend analysis done by them indicated that 60 % of the worlds heart disease population, including CHD, would live in India by 2015.19.There are no detailed reports on CVD mortality by the Indian government. WHO has predicted that from years 2000 to 2020 DALYS from CHD in India shall double in both men and women from 7.7 and 5.5 million respectively.

India lacks data on cardiovascular risk factors obtained from prospective cardiovascular epidemiological studies. However multiple case control studies exist. The largest of these case control studies is the INTERHEART study [16]. This study reported that standard risk factors such as smoking, abnormal lipids, hypertension, diabetes, high waist hip ratio, sedentary life style, psycho-social stress and lack of consumption of fruits and vegetables explained more than 90% of acute CHD events in South Asians. In our study we intend to evaluate the role of infection as a risk factor in addition to the assessment of the standard risk factors.

As per Vamadevan S.Ajay and Dorairaj Prabhakaran India is in the midst of the triple burden of diseases, the unfinished agenda of communicable disease linked with life style changes and emergence of new pathogens and overstretched health infrastructure. Hence through our study we intend to find the role of these infectious diseases through a circulating marker called heat shock protein-60 in causing plaque disruption in ACS patients.

8. Pathophysiology of Coronary Atherosclerosis and Acute Coronary Syndrome:

Carl Rokitansky and Rudolph Virchow ,in the mid 19th century discovered the role of inflammation in atherosclerosis [12]. Rokitansky suggested that the intiating step of atherosclerosis was caused by the accumulation of blood derived products in the arterial wall and inflammation was caused by the accumulation of blood derived products in the arterial wall and inflammation was the reaction to the accumulated lipids [12]. Rudolph Virchow ,in turn, suggested that the inflammatory reactions were the preliminary step [12]. In the 1970's Russell Ross proposed the response to injury hypotheses highlighting endothelial injury, smooth muscle cell growth and lipid hypotheses in atherosclerosis [13]. Thus atherosclerosis is seen as an inflammatory disease including various cell types and lipoprotein metabolism.

Although the inflammatory reactions are accepted to be involved in all stages of atherosclerosis progression, the debate on the initiating step is still on-going.

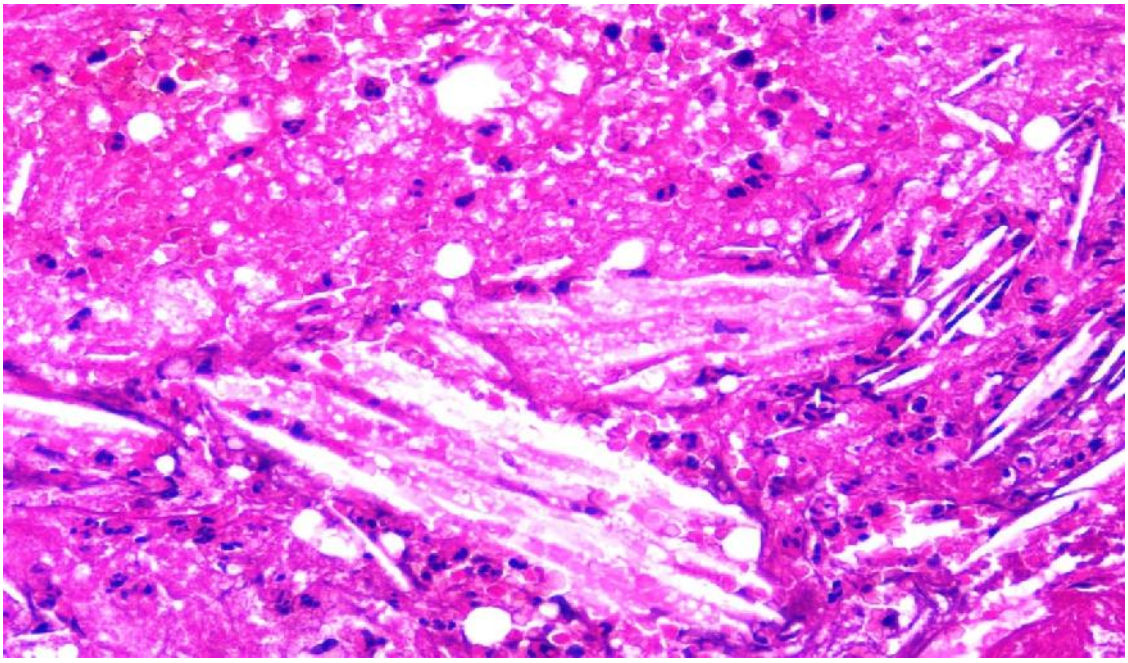
Our study is aimed at focusing infection as the initiating step of inflammation which can casue or aggravate atherosclerosis leading to ACS.

9. Atherosclerosis and Thrombus formation:

Atherosclerosis usually develops in the context of elevated risk factors.

Figure 1

Figure 2



SCHEMATIC EVOLUTION OF ATHEROSCLEROTIC PLAQUE

Accumulation of lipoprotein particles in the intima

↓

Oxidation and glycation of these particles

↓

Local oxidative stress increases

↓

Local cytokine /circulating elevation of cytokines causing inflammation

↓

Leukocyte migration into intima by increased expression of adhesion molecules for leukocytes and chemoattractant molecules

↓

Monocytes enter artery wall in response to cytokines(il-8,mcp-1)

↓

Form macrophages by action of macrophage colony stimulating factor and augmented expression of scavenger receptors on macrophages (e.g.CD163)

↓

Uptake of modified lipoprotein through these scavenger receptors and form foam cells

↓

Small areas of endothelial desquamation occurs leading to microthrombi formation

↓

Platelets in microthrombi form mediators for SMC migration(PDGF),collagen synthesis(TGF-BETA) and inhibit fibrinolysis

Foam cells produce cytokines, HOCL, superoxide anion and MMPS

↓

Smooth muscle cells migrate into intima from media and divide and form fibro-fatty plaque with lipid laden macrophage debris and extracellular lipid- cholesterol esters and cholesterol monohydrate crystals

↓

Calcification can occur and fibrosis continues accompanied by SMC death

Leading to protective fibrous cap production

↓

Neo vascularisation occurs in response to acid fibroblast, vascular endothelial growth factor—breeches in the vessels cause micro thrombosis(marked by hs -CRP)

↓

Collagen accumulation and increase in size of thrombus

↓

Those with fissured fibrous cap, numerous mononuclear phagocytes, large lipid pools

↓

Increased macrophages tend to have increased tissue factor

↓

Local denudation of endothelial cells occurs with or without intact endothelium

Apoptosis of endothelial cells is promoted by inflammation

Endothelial cells express MMPS in response to oxidized lipids/oxidative stress and inflammatory mediators

Local cholesterol crystallization in relation to shear stress promotes activation of NLF3 pathway and increases inflammation (il-1)

Plasmin generated by PA degrade components of arterial extracellular matrix and activate MMP-2

Proteolysis causes fracture of cap

Decreased de novo synthesis of smc and hence collagen decreases leading to plaque destabilization

T cells are activated in thrombus release IFN-GAMMA which decreases collagen synthesis by smc and trigger smc apoptosis

** Oxidative stress and inflammatory pathways play a decisive role in destabilization of the plaque that triggers thrombosis in both superficial erosion and fibrous cap rupture.

↓

Plaque ruptures or erodes and coagulation cascade starts and forms thrombus

10. ACUTE CORONARY SYNDROME:

As influenced by various risk factors, the instable plaque on disruption forms thrombus breaking the coronary artery and causing acute coronary syndrome with STEMI on ECG. Clinically these cases present with prior symptoms of Angina pectoris, or other peripheral vascular diseases like having intermittent claudication.

During the acute episode, the chest pain that occurs is classically an exaggerated version of angina pain where the patient is unable to even move in the bed and has a feeling of loss of life, vomit and defecates. The pain is retrosternal, radiating to left arm commonly but can radiate to any part above umbilicus and below the jaw. This pain is due to activation of nerve endings from dying myocardium. Cold sweats, palpitations, giddiness and sudden severe weakness can be a part of the presenting symptomatology. The pain of MI, before presentation has to be differentiated from

1. Pleural pain
2. Pulmonary embolism
3. Acute aortic dissection
4. Oesophagi is/Gastritis
5. Costo chondritis
6. Pericarditis

However, clinicians have to keep an entity called silent MI in mind, especially while dealing with diabetes and hypertensive group of population. These patients outcome is however no different from the other STEMI cases

Physical Examination:

These patients look conscious and have a rolled fist at their chest, a clinical sign known as the divine sign. However, when patient has massive MI, involving the majority of left ventricle, these patients present with severe dyspnoea and will be uable to lie down flat. Similarly patients who present with cardiogenic shock are presenting a total calm attire with no movement and have a pallor at the cord extremities and face and have cyanotic nails and lips.

These patients have a heart rate elevation, however can also present with total absence of pulse or bradycardia. Many patients without complications of STEMI have normal blood pressure. Patients. Patients can even present with elevated blood pressure due to worry, which leads to pressures greater than 160/90mmHg. These patients due to LV dysfunction, inspite of having hypertension earlier can present with low BPand for these patients to return back to their hypertensive range will take three to six months post MI. when patients are in shock, their BP may fall to undetectable levels. This hypotensive presentation is more common with inferior wall MI, due to parasympathetic activation. The body temperature may rise and the patient can have fever which lasts for four to five days. The elevation of body temperature can be a part of inflammatory processes in the body.

When the infarction involves the right ventricle, on examination of the neck veins, the juglar vein is distended and feature of tricuspid regurgitation like elevated a-v wave is evident. The prominence of a wave as a feature of LV dysfunction causing pulmonary hypertension can occur in STEMI patients. The carotid pulse has to be palpated to evaluate,

1. Severe LV dysfunction- pulse alterations
2. Mitral regurgitation/ ruptured ventricular septum- sharp upstroke which is short in duration.

The auscultatory findings were used by Kimball and Killip in 1967 to classify patients into the following classes which explains us the mortality rate in cases, with class IV having the worst prognosis

Killip Class I- No features of pulmonary edema, hemodynamically stable

Killip class II- pulmonary edema evident by basal rales on auscultation

Killip class III- with complications,S3,pulmonary edema(>10cm from diaphragm rales+)

Killip class IV – cardiogenic shock

Systemic Examination:

Palpitation in uncomplicated cases is insufficient but at times reveals S3 and S4. On auscultation, S1 (first heart sound) becomes soft and sometimes a reversal splitting of second heart sound occurs. S3 and S4 are heard in patients with severe LV dysfunction and are heard the best in the mitral area. When the MI occurs in the right ventricle S3 and S4 are best audible in the left lateral sternal border. An holosystolic murmur is heard at the apex radiating to axilla and back due to dysfunction of the papillary muscle and causing mitral regurgitation. Doctors should also concentrate on the auscultatory findings of ribs of pericardium due to all strata infarction.

Palpation of the abdomen may reveal congestive hepatomegaly, but always there need not be an increase in the size of the liver. Patients can have altered sensorium or neurological weakness secondary to embolic phenomenon. Examination of fundus for changes secondary to hypertension or diabetes has to be assessed.

ECG Findings:

STEMI as above is defined for classification , but the location of blocked artery can be assessed by lead involvement.

Left anterior descending artery:

It is one of the major branches from the left coronary artery and gives rise to first diagonal branch and the latter to first septal branch. Occlusion of LAD before these branches arise give rise to ST elevation in leads V1-V4 and leads I and aVL. It can be associated with RBBBand at times with ST elevation in leads aVR. Blockage of LAD between diagonal and septal branch causes STEMI changes in V1 to V4

Figure 3

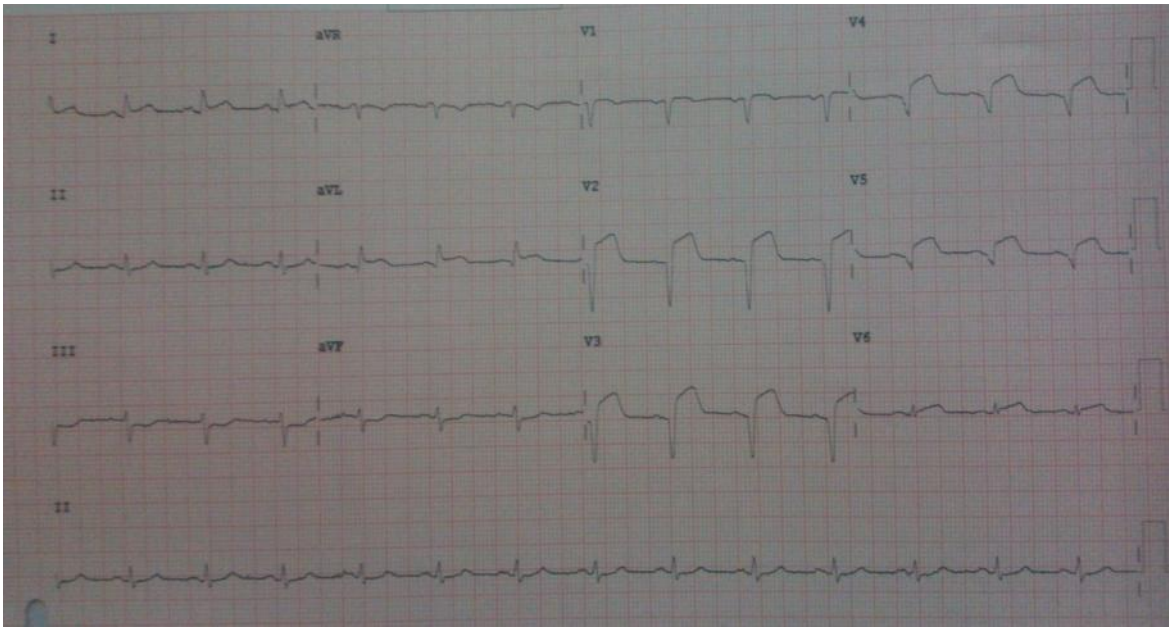
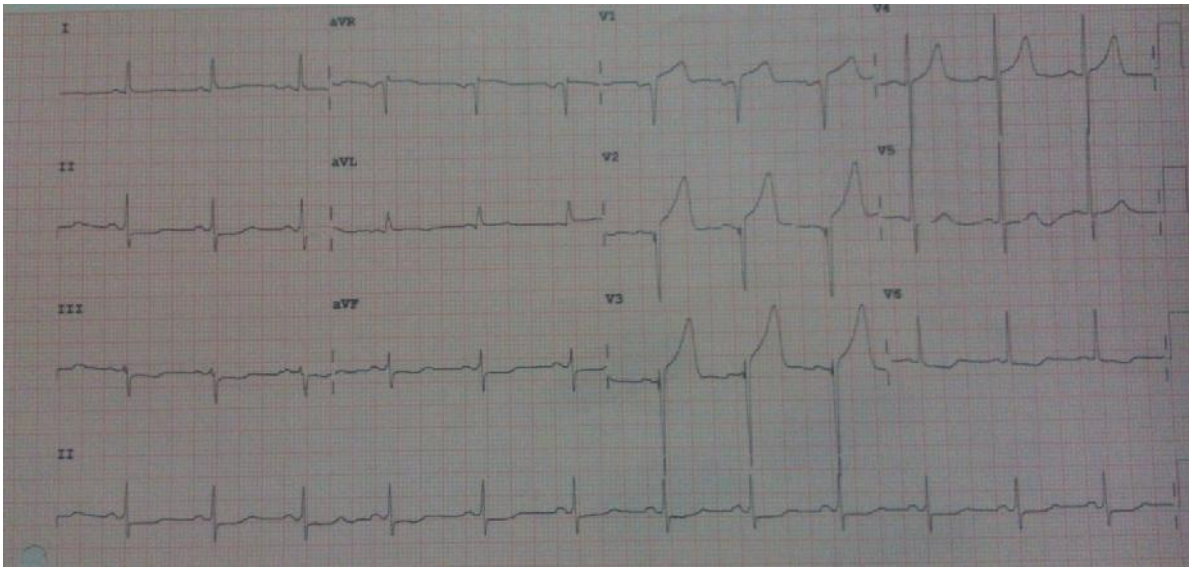


Figure 4



Complications of Anterior wall MI

1. Ventricular fibrillation/ Ventricular Tachyarryhthmias
2. Intraventricular conduction defects
3. Right bundle branch block
4. Left bundle branch block
5. Complete AV block
6. LV dysfunction and heart failure
7. Sudden cardiac death.

Left circumflex Artery:

When thrombosis occurs in this artery ST elevation occurs in leads aVL and I or V5 and V6 with reciprocal changes in V1 to V3. When LCX supplies or becomes posterior descending artery ST elevation is seen in II, III and aVF showing involvement of inferior wall.

When posterior wall is affected, ST depression is seen from V1 to V3 with tall R wave in V1 and V2 and leads placed in V7, V8 and V9 show ST elevation. In the definition of STEMI only exception to height of elevation is seen in this type of MI, where even an elevation of 0.5mm is considered to be STEMI, as the heart is distant from these leads V7-V9 which picture the posterolateral aspect of the heart.

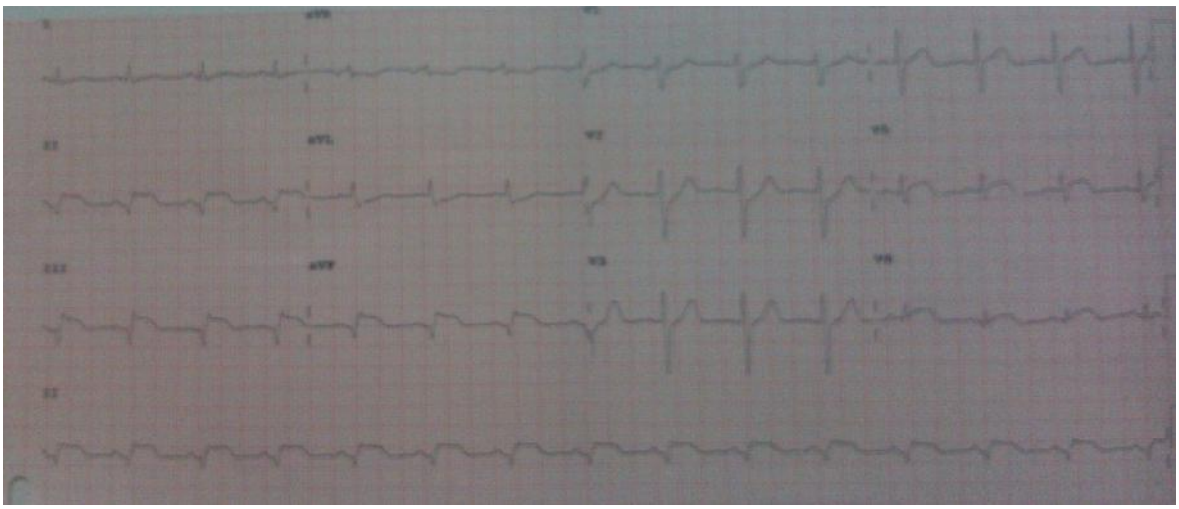
Complications of Posterolateral/Lateral STEMI:

1. Ventricular Fibrillation and ventricular Tachycardia
2. Left ventricular Dysfunction
3. AV block, when the dominant artery of the heat is left circumflex artery

Right coronary artery:

Plaque rupture and occlusion of this artery causes inferior wall MI seen as ST elevation in leads II, III and aVF at times with V5 and V6 involvement. When reciprocal changes are seen in V1, V2 and V3 the possibility of posterolateral MI has to be ruled out.

Figure 5



Complications of inferior wall Mi:

1. Varying degrees of atrioventricular block is commonly seen
2. Ventricular tachycardia , ventricular fibrillation – rare
3. Intraventricular conduction defects – LBBB, RBBB with associated greater incidence of asystole, atrioventricular block, ventricular fibrillation and cardiogenic shock. All these features are associated with extensive involvement of myocardial tissue.
4. Acute severe mitral regurgitation secondary to rupture of posteromedial papillary muscle, as this is supplied by right coronary artery only. This is a very serious condition.
5. Right ventricular STEMI: Whenever we find inferior wall MI, right sided ECG has to be taken to check STEMI in right sided leads of ≥ 1mm. As the changes of right ventricular MI last only for a transient period of approximately one hour, it should be mandatory to take right side ECG in all cases of inferior wall MI. The hemodynamic abnormality seen in right ventricular MI can be hypotension with distended neck veins (jugular vein) and lungs without crackles. These set of patients have positive Kussumaul sign.

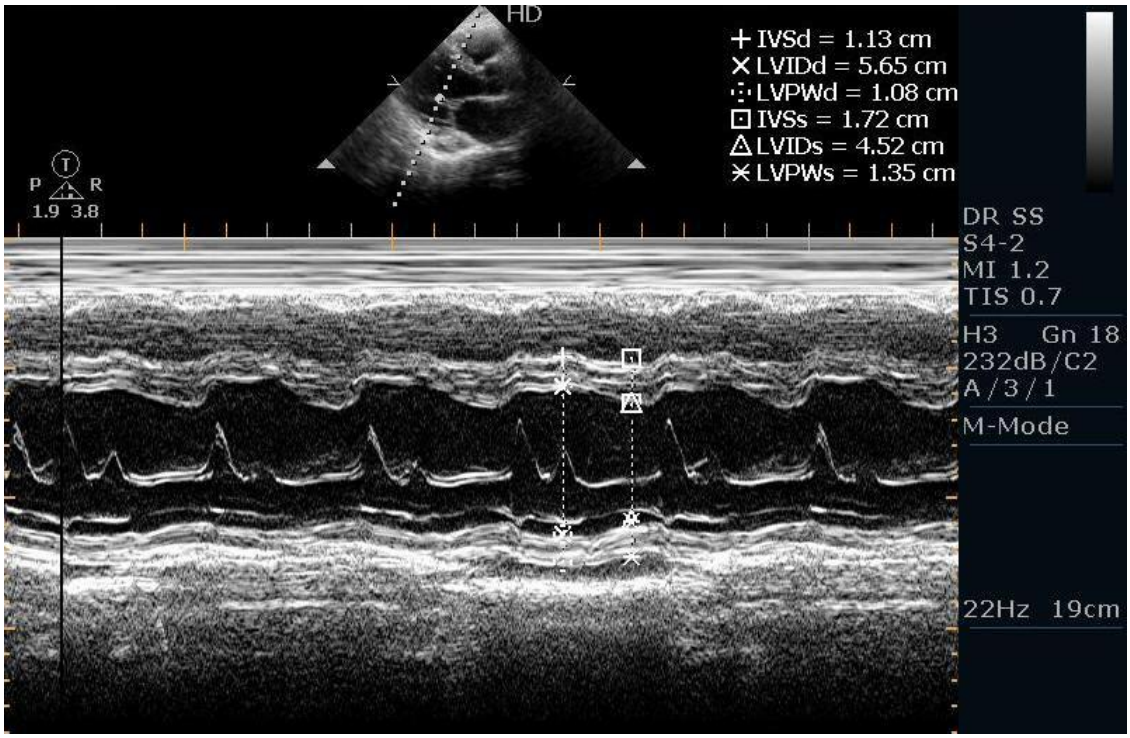
Investigations:

1.Routine blood investigations like complete blood counts, serum creatinine, blood urea, blood sugars, serum fasting lipid profile

2.Urine routine

3.Cardiac biomarkers like Troponin T, CK-MB

4.Echocardiography – Figure 6



Treatment:

1. Thrombolytic therapy
2. Loading dose with high dose antiplatelet and statin
3. Anticoagulation with unfractionated heparin or low molecular weight heparin based on presence of complications like LV clot, pulmonary embolism
4. For ongoing pain – nitroglycerin (when BP > 90 mm Hg & pulse rate > 50 beats/min)
5. Supplemental oxygen therapy
6. Morphine sulphate for pain relief
7. Beta blockers in the absence of complications like prolonged pr interval,av conduction block, bradycardia.

8. ACE inhibitors/ARBS
9. Diuretics in case of failure or fluid overload stages
10. Percutaneous coronary intervention – primary or elective.
11. Intraaortic balloon pump therapy
12. Intraventricular conduction devices
13. Newer drugs like ivabradine, vasopressor, inotropes are other treatment options based on clinical presentation.

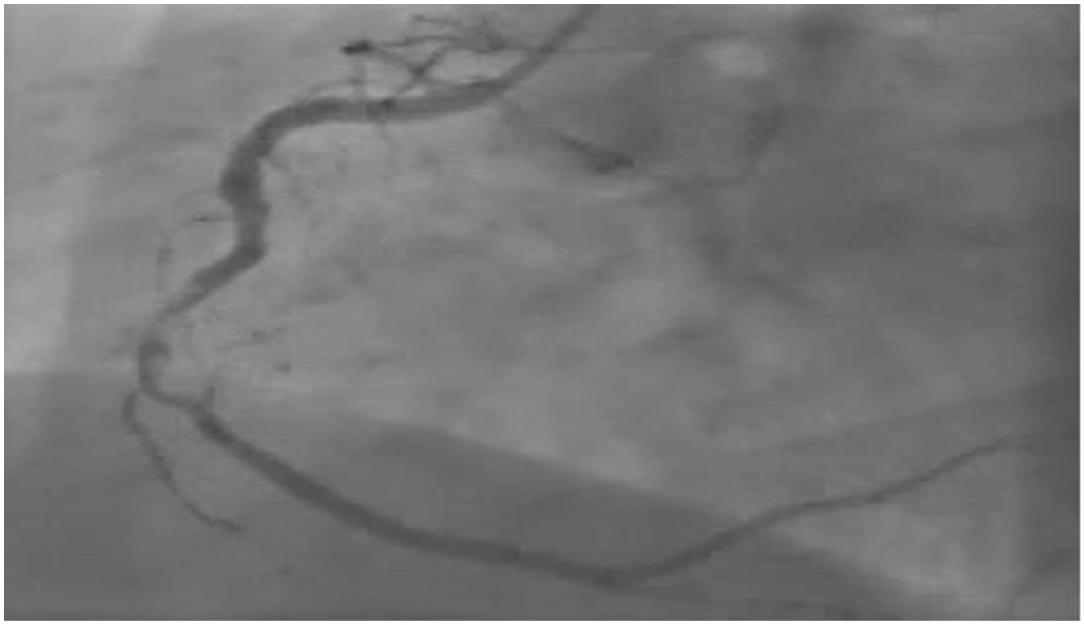


Figure 7a & b

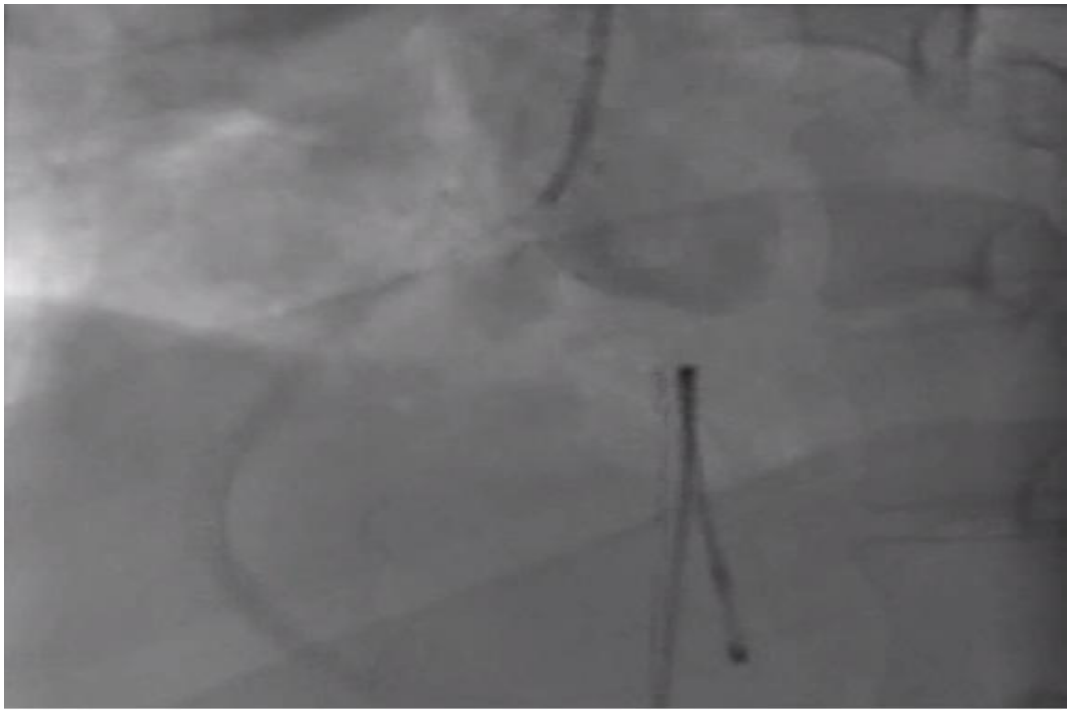


Figure 7c

Figure 7d

11.Risk Factors for Atherosclerosis and ACS:

A risk factor refers to any attribute characteristic or exposure of an individual, which increases the likelihood of developing a non communicable disease.

As per the INTERHEART study the attributable traditional risk factors for ACS are hypertension, diabetes mellitus, dyslipidemia, elevated waist hip ratio, obesity, smoking, alcohol consumption, decreased physical activity, decreased consumption of fruits and vegetables, psycho social stress incidence is elevated in Indian population.

RISK FACTORS Tab.1

Traditional Risk Factors
Atherogenic diet
Obesity
Age
Gender
Family History
Diabetes Mellitus
Systemic Hypertension
Dyslipidemia
Smoking/ Alcohol
Stress
Physical Activity

Novel Risk Factors
Lipoprotein a
Inflammation
Infection
Oxidative stress

In our study we intend to evaluate all the traditional risk factors through standard definitions and scales as given below,

- Current Smoker or tobacco user : Person who smokes either daily or occasionally
- Current Daily Smoker or tobacco user : Person who smokes either daily or occasionally except on special religious occasions
- Past Smokers : Persons who have stopped smoking from past 12 months
- Non-Smoker : Person who has never smoked in their life time
- Current Drinker: Person who drinks daily or occasionally in the past one year
- Former Drinker: Person who had not consumed alcohol daily or occasionally in the past one year but has consumed prior to it
- Complete Abstainer: Person who has never consumed alcohol
- Binge drinker : Person who drinks alcohol daily of more than five drinks in case of men and more than four drinks in case of women
- A drink is defined as standard drink if ethanol content is more than 10gm
- Dietary habits: As per 24 hour recall method (questionnaire attached below)
- Physical Activity : IPAQ method of assessment (attached below)

  1)Inactive : No physical activity

2) Minimally active : 3 or more days of extensive activity for a minimum of 20 minutes every day

Or 5 or more days of moderate activity atleast for 30 minutes per day

3)HEPA activity : Vigorous activity spending 1500 MET minutes/week

- Metabolic Equivalent (MET): It is calculated as a ratio of individual's metabolic rate between his activity rate and resting rate.

  1) At rest MET : It is equal to spending 1kcal/kg/hour

  2) At working MET: It is equal to spending 4kcal/kg/hour

  3) At vigorous activity MET : It is equal to spending 8 kcal/kg/hour

- Central Obesity: It is defined based on the waist circumference and hip circumference and the ratio between two or the waist circumference alone.

  Central obesity is calculated based on measuring this value in the mid axillary line between the inferior coastal margin and superior iliac crest with a foldable tape.

  As per ATP III guidelines:

  >102 cm in males

  >88 cm in females

  As per South Asia Pacific Guidelines:

  >90 cm in males

  >80 cm in females

  Weight is classified as follows as per WHO guidelines,

- Underweight : A person is said to be underweight when the BMI <18.5kg/m2
- Normal Weight :A person is said to be normal weight when the BMI between 18.5 and 24.9kg/m2
- Overweight : A person is said to be overweight when the BMI is > 25 kg/m2-29.9kg/m2

- Obesity : A person is said to be obese when the BMI is >30kg/m2
- Hypertension : In simple terms it is elevated blood pressure.In our study we considered blood pressure to be elevated when patient is a known hypertensive on antihypertensive medication or has blood pressure of systolic/diastolic >140/90mmHg

Tab.2

Stages of Blood Pressure	SYSTOLIC/DIASTOLIC
Stage 1 Hypertension	≥140-159 / ≥90-99
Stage 2 Hypertension	≥ 160 / ≥100

- Diabetes mellitus: When overt hyperglycemia manifestations are absent diabetes is defined as per ADA 2013 guidelines if,

  1) HbA1C ≥6.5

  2) FBS ≥ 126mg/dl and PPBS ≥ 200mg/dl

- Dyslipidemia: AHA 2013 guidelines are followed for ASCVD risk factor assessment and defining dyslipidemia

Individuals

1. Clinical manifestations of vascular disease,
2. Initial elevations of LDL–C >190 mg/dL,
3. Diabetic patients (age group 40 to 75 years) with LDL–C 70 to189 mg/dL and without clinical vascular disease, or
4. Without clinical ASCVD or diabetes with LDL–C 70 to189 mg/dL and ASCVD risk >7.5%

Clinical ASCVD is said to be clinical evidence of peripheral arterial disease, coronary vasculature diseases or cerebral vasculature disorders. All inclusive apart from genetic or hereditary lipoproteinemias.

However these are the recent guidelines, but we have considered ATP III guidelines in our study where

Tab.3

LDL	**INFERENCE**
<100	Normal
100-129	Near Normal
130-159	Borderline elevation
160-189	Elevated levels
>190	Very elevated levels

HDL cholesterol levels of <40 are considered low while levels >60 are considered as high.

Tab.4

TRIGLYCERIDES	
<200	Normal
200-239	Borderline elevated
>240	High

When risk factors are present these interventions are taken into consideration based on those coronary heart disease risk factors

1) Cigarette smoking

2) Hypertensive >140/90mmHg or on antihypertensive medication
3) Low HDL <40
4) Family History of Coronary artery disease where first degree male relatives have coronary heart disease by <55yrs and similarly first degree related women of age <65 years age

Based on these risk factors dyslipidemia can be inferred as follows. Usage of Framingham risk score based on these risk factors can also be taken into consideration.

Tab.5

Risk Categorisation	**LDL levels**
CAD or CAD risk equivalents	≥ 100mg/dl
2 or more risk factors	≥130mg/dl
0 or one risk factor	≥160mg/dl

- Psycho social stress: Gold berg scale (bedside test where set of questions are asked)

Tab.6

POINTS	**ANSWERS**
0	Not felt so
1	Feels a bit so
2	Somewhat feels so
3	Feels intermediately so
4	Feels quite a lot like that

Tab.7

TOTAL SCORE SUMMATING ALL ANSWERS	INFERENCE OF LEVELS OF DEPRESSION
0-9	NO
10-17	POSSIBLE
18-21	MINIMAL
22-35	MILD – MODERATE
36-53	MODERATE
54 & ABOVE	SEVERE

As per Integrated disease surveillance project of non communicable disease risk factors survey in Tamil Nadu done in 2007 – 2008 by ICMR concluded that smoking is the leading risk factor for non communicable dieases in Tamil Nadu and that physical inactivity is the leading casue for hypertension, diabetes mellitus and coronary artery disease [6].

An review of traditional risk factors in CAD and evaluation of novel risk factors like lipoprotein a, oxidative stress, infection and inflammation is essential to define the reason for early onset of plaque destabilization in young population.[1,3,12.]

Lipoprotein a denotes a subclass of LDL characterized by an apo B moiety covalently bound to apolipoprotein a.apo B is the initiating molecule in atherosclerosis plaque formation. Genome –wide association studies and mendelian randomization studies support a causal role for Lpa in atherothrombosis [12].

Oxidative stress through oxidation of LDL has a proven role in the pathogenesis of atherosclerosis. Inflammatory cells in the plaques especially macrophages contain enzyme myeloperoxidase can generate potent oxidant species like hypochlorous acid and

mediate tyrosyl residues chlorination in lipids. Such modification causes production of oxidized lipids which are taken up by macrophages and can also impede reverse cholesterol transport mediated by HDL [12].

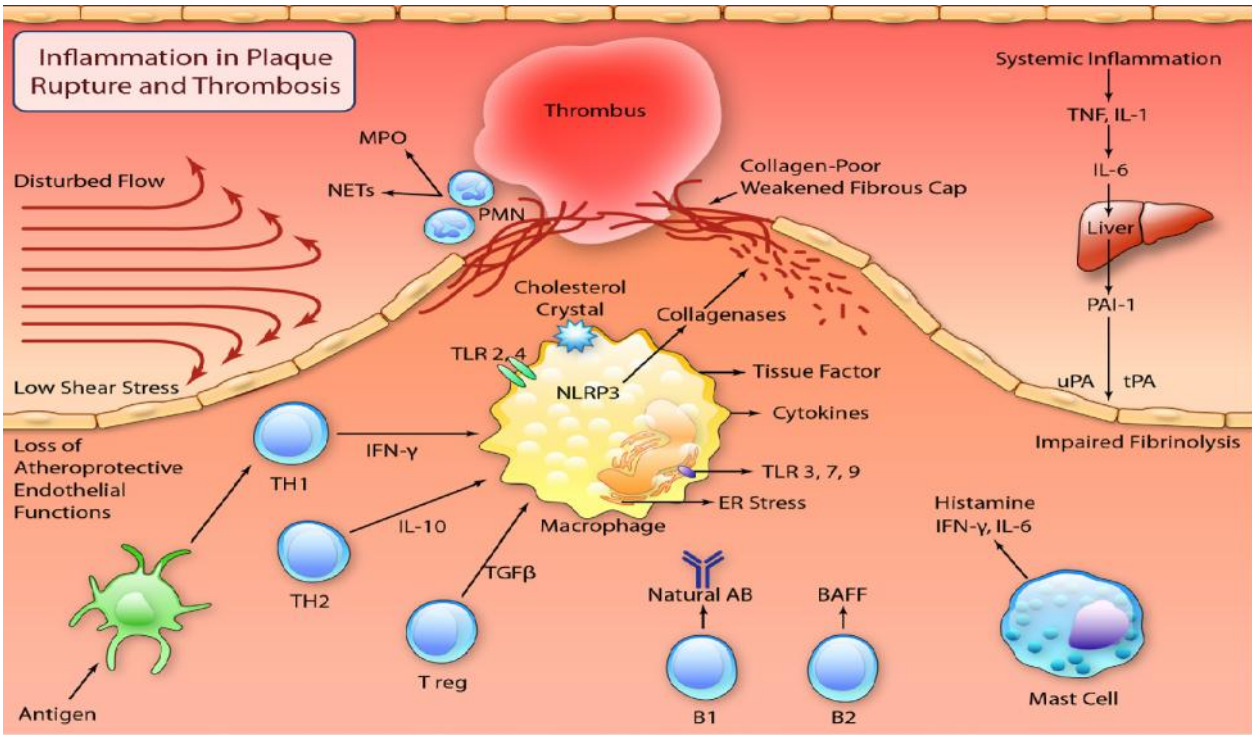
The other novel risk factors as inflammation and infection are discussed in detail in below sections. In our study we are aiming to evaluate the traditional risk factors in our study and control population through above standardized methods and find the dominant risk factor in people visiting our hospital. Along with these non modifiable risk factors for ACS like age and sex are also planned to be evaluated in our study.

11. Role of Inflammation In ACS:

A growing body of evidence points to inflammation as a primordial driver of all stages of atherothrombosis. Peter Libby and Filippo Crea clinical review on JUPITER trial highlighted the fact that people in the group with below median LDL and below median C-reactive protein had no demonstrable benefit from statin treatment while the group with below median LDL and above median C-reactive protein enjoyed the benefit from statin therapy, highlighting the importance of inflammation in the absence of overt dyslipidemia in cardiovascular diseases.27.Filippo Crea and Giovanna Liuzzo in their paper on pathogenesis of ACS stated that in patients with ACS and systemic evidence of inflammation had widespread coronary inflammation evidenced by activation of neutrophils in the cardiac muscle not supplied by the artery responsible for ACS. This feature is not seen in coronary atherosclerosis or recurrent ischemia causing chronic stable angina and multivessel coronary disease or in vasospastic angina patients.9.Hence they highlighted the fact that the widespread acute coronary inflammation is the likely cause for, multiple stenoses, multiple thrombi and multiple fissured plaques involving different coronary artery branches. This fact is proven by many angiography and

intravascular imaging studies which had even measured the circulatory inflammatory markers.28-31.Such concept of ACS with obstructive atherosclerosis and systemic inflammation is confirmed by postmortem studies.

Figure 8



As discussed above two mechanisms precipitate ACS, a rupture of the plaque's fibrous cap and superficial erosion of the intima. The former mechanism being most fatal.56

Antigens + Dendritic cells

↓

Activate TH1 lymphocytes

↓

Produce IF gamma

↓

Activate macrophages which have TLP 2 & 4, which

Bind to damage associated molecular pattern and pathogen

associated molecular patterns

↓

Release of proinflammatory cytokines

↓

Plaque ruptures and forms red thrombus

↓

Polymorphonuclear leukocytes in thrombus increase oxidative stress(MPO) and mast cells release il-6 and IFN-gamma

↓

Trigger systemic inflammation and hepatic acute phase response

↓

High sensitivity C- reactive protein

A study highlights the fact that advanced plaques have a defect in the clearance of apoptotic cells leading to their accumulation ,a process called mummification because of a defect in efferocytosis. These cells release procoagulant tissue factor which triggers thrombus formation in the disrupted plaques [33].

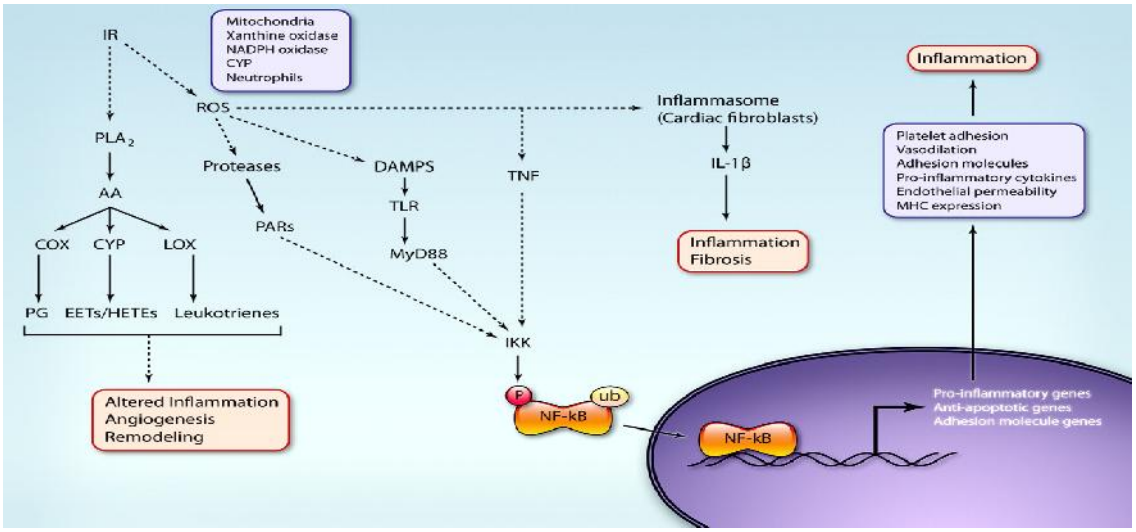
Peter Libby, Ira Tabas, Gabrielle Fredman and Edward A. Fisher highlighted the importance of specialized pro resolving medications(SPMS) which play an important role in resolution of inflammation without causing immune suppression by reducing efferocytosis in atherosclerotic plaque and thus by avoiding ACS.

Through our study we intend to prove the role of systemic inflammation irrespective of lipid abnormalities, which is provoked by chronic infection causing release of heat shock protein -60 which acts as DAMP and augments atherosclerosis to ACS.

12. High Sensitivity C-Reactive Protein and Atherosclerosis:

C-reactive protein is a pentraxin acute phase protein, members of which are evolutionarily conserved in most vertebrates [40]. CRP is produced by hepatocytes, smooth muscle cells and macrophages in response to inflammatory cytokines including IL-1 and IL-6.Ehrin J.Armstrong, David A.Morrow and Mark S.Sabatine have stated in their paper that CRP is a stable clinical marker because of its stability, reproducible results and ease of assay. They also stated that CRP remains elevated for upto 3 months in one set of ACS patients and other set shows slow decline during hospital stay itself. Sano T et al have stated that in ACS patients the CRP levels correlate with the presence of plaque rupture, as assessed by intravascular ultrasound [41].

Figure 9



Crea et al stated that the number of disrupted coronary plaques correlates with systemic hs-CRP levels and found that in ACS patients most of the times admission values of ≥ 10 mg/dl.

In the PROVE-IT TIMI 22 trial it was found that patients treated with statin had decreased hs-CRP values compared to admission values and had decreased mortality and all these effects were independent of cholesterol levels [42]. Excluding the conditions as stated in the exclusion criteria for elevated inflammation and elevated hsCRP [,43,44] we would like to study the level of systemic inflammation in ACS cases and control population. As stated in the US National Library of Medicine and National Institutes of Health apart from CAD, CRP can be elevated in the following conditions which we will be considering as exclusion criteria in both our cases and controls.

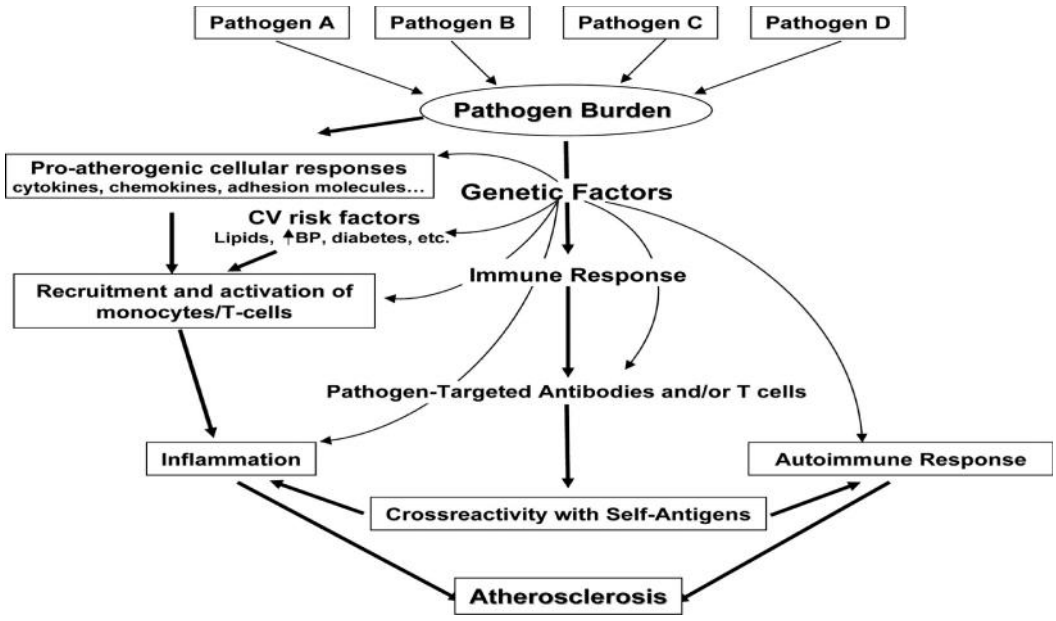
- Malignancy
- Connective tissue disorders
- Inflammatory bowel disease – Crohn's Disease, Ulcerative Colitis
- Pneumococcal pneumonia – community / hospital acquired

- Acute Rheumatic fever
- Joint abnormalities as Rheumatoid arthritis
- Pulmonary/Disseminated Tuberculosis
- History of intake of oral contraceptive pills in the past 6 months
- Pregnancy-3rd trimester.

13. Infection in Atherosclerosis:

Among the emerging risk factors, infectious agents both bacterial and viral agents have received periodic attention as promoters of atherogenesis through the decades. According to Peter Libby, Paul M Ridker and Kevin Croce, infectious agents might not be involved directly in atherogenesis through local actions in the plaque but a inflammatory response against these infections tips the homeostatic balance which favors the thrombosis and decreases fibrinolysis through elevated production of IL-6,plasminogen activator inhibitor-1.12.Such elevation of inflammatory cytokines causes elevation of hsCRP a systemic marker of inflammation as discussed above.

Figure.10



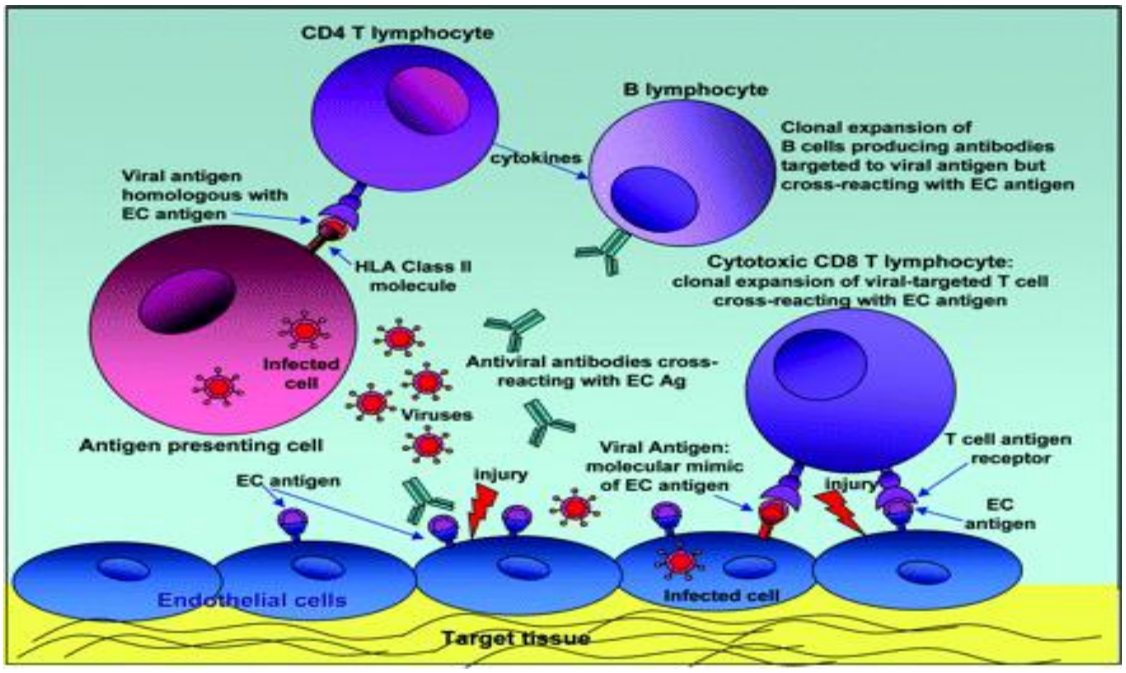
As written by Fiorella Calabrese et al in their editorial infectious agents causing atherosclerosis plaque formation or rupture through activation of innate immunity mechanism via Toll like receptors and activation of adaptive immunity via T cell specific for antigens such as Chlamydia pneumonia, heat shock proteins or oxidized lipoproteins [52].

As per Stephen E .Epstein et al, various pathogens like Cytomegalo virus, Herpes Simplex virus types 1 & 2,Chlamydia pneumonia and Helicobacter pylori, Hepatitis A Enterobacteriaceae sps and periodontal pathogens to were found to reside in human atherosclerotic plaques and seroepidemiological studies demonstrated an association between pathogen specific antibodies and atherosclerosis [51]. Pathogens always need not reside in the body or in the plaque to cause atherosclerosis. The memory cell effect secondary to infection and the autoimmune mechanisms and the propogation of inflammatory cascade initiated by these agents is sufficient for atherosclerosis to occur in human body.[51,53.]

This explains the fact why many antibiotic trials where antibiotics have been prophylactically been given failed to prevent the occurrence of ACS. They are the ROXID, STAMINA, AZACS, ANTIBIO trials which showed no benefit with prophylactic antibiotics from preventing ACS. Epstein et al in their review article on infection and atherosclerosis concluded that infection contribute to atherogenesis and its acute complications ,however this in turn is determined by the hosts response to infectious agent, the pathological burden of infectious agent the magnitude of host inflammatory response to infectious agent and whether a host is predisposed to develop an autoimmune response. In our study we intend to check the hosts level of infection and the inflammation caused by it which is hypothesized to be responsible for ACS. The

contribution of traditional risk factors in causing ACS has been planned to be evaluated in our study to check the power of infection alone as risk factor for atherosclerosis. Such studies are not done in our nation in South India, hence we intend to take this study.

Figure 11

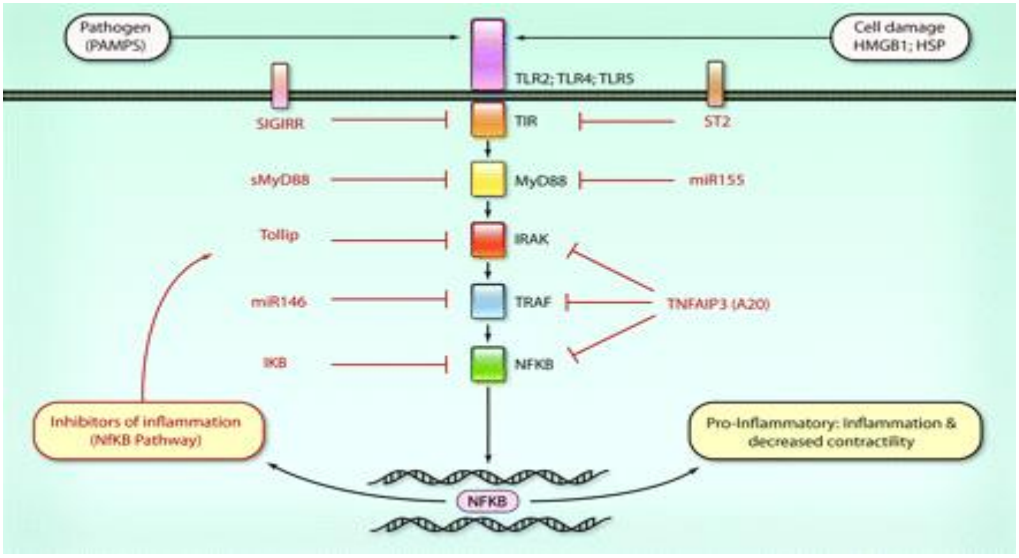


14. Heat Shock Protein 60 as a marker for Chronic Infection in ACS:

Heat shock protein is a family of chaperone proteins with strong antigenic properties with immunogenic and proinflammatory properties[56]. This stress protein is a nuclear encoded protein found primarily in mitochondria[54]. M.Rabozynski in their study a statistical significance between atherogenesis and elevated circulating antibodies to hsp60 [57]. They explained that heat shock proteins are phylogenetically old cellular protection system, which protects proteins from denaturation, determining the high conservation of the amino acid structure of these proteins, which explains the homology of these proteins of >70% in prokaryotes and humans. This homology enables the possibility of cross reactive immune response to bacterial antigens with antigenic hsp of

human cells.Iruna Cohen in 1990 and Wick et al first explained this concept of antigenic mimcry.[58,59.]

Figure 12



Although viruses do not express HSPs, as they proliferate within their host cells and then break though host cell membrane to continue their life-cycle, host proteins can be incorporated within the viral membrane.64,65. If such proteins include HSPs, as has been shown, this would provide an explanation of how viruses, in addition to bacteria, could evoke a HSP-based autoimmune response in the host.

Hence when once infected with bacteria and viruses with hsp60 body produces antibodies to them. In conditions like increased shear stress, on exposure to nicotine, elevated sugars, elevated temperature, the intracellular conserved human HSP 60 comes to the surface because of the prokaryotic molecular mimicry the immune system recognizes this human HSP 60 as pathogenis inview of earlier infection memory and binds with it. As HSP 60 is expressed on endothelial cells, antigen presenting cells, T cells and B cells all these are activated and the inflammatory cascade is set into force enhancing plaque rupture and leading to ACS.A study by Zhang et al, identified a strong

correlation between circulating levels of HSP 60 and the risk of CHD.54.Another study by Luigi M Biasucci et al concluded that seropositivity for HSP 60 appeared to be highly sensitive and specific marker for ACS independent of hs CRP and troponinT.56.Zhang et al have found a positive correlation between hsp-60 and antibodies to hsp-60 in coronary artery disease in Asian population. When detectable HSP 60 values are categorized as two groups with low HSP 60(<1000ng/dl) and high HSP 60(>1000ng/dl).56. As India is a country with elevated infectious disease burden and ACS we want to evaluate the relation between these two conditions in our study as there are no studies in South India based on HSP 60,hsCRP and ACS.

Study Area : PSG Hospital, Coimbatore

Study Population:

- Cases : STEMI patients diagnosed and being treated in PSG hospital
- Controls : Subjects visiting master health check up in PSG hospital without evidence of acute coronary syndrome as per clinical symptoms and ecg findings(as mentioned in the review of literature)

Study Time:

- As the samples for HSP 60 molecule can be stored for a maximum duration of 70-80 days.The study collection of samples was done in that stipulated time.The analysis of literature and molecule search and attainment of molecule with laboratory standardization took the rest of the time.

METHODOLOGY

Case Control Study

PSG Hospitals

↓

CASES(30-40)	**CONTROLS(30-40)**
Patients diagnosed as STEMI satisfying the inclusion criteria	Master health check up & visiting subjects without ACS
Clinical History,	Clinical History,
Clinical Examination details,	Clinical Examination details,
Evaluation of traditional risk factors,	Evaluation of risk factors,
Measurement of circulating hs-CRP & HSP-60 values,	Measurement of circulating hs-CRP & HSP-60 values

Evaluation of Echo cardio graphic findings*,

Evaluation of per cutaneous coronary intervention findings(PCI)*

*Done by Cardiologist in PSG hospitals

Inclusion Criteria:

Age: 20-80 years

Patients diagnosed to have STEMI with,(CASES)

- Symptoms clinically consistent with STEMI lasting >30 min
- Arrival at hospital within 12 hour of onset of chest pain
- ECG findings with new ST elevation from the J point in two contiguous leads with ≥0.1 mV in all leads except in leads V2-V3 where this features are applicable - ≥0.2mV in ≥40 years men and ≥0.25mV in < 40 years men or ≥ 0.15 mV in women.

Controls will be subjects with,

- No symptoms of Acute coronary syndrome
- No features of Acute coronary syndrome on ECG (in the absence of LVH and LBBB)
- ST depression and T wave change - New horizontal or down-sloping ST depression ≥0.05 mV in two contiguous leads and/or T inversion ≥0.1 mV in two contiguous leads- R/S ratio > 1 or prominent R wave.

Exclusion Criteria:

Pregnant females

Patients with

- Previous or recent ACS in past 3 months
- Severe Renal dysfunction

- Concomitant inflammatory diseases (e.g. Rheumatoid arthritis, Inflammatory bowel disease)
- Patient on immunosuppressive therapy
- Malignant tumor patients on chemotherapy and immunomodulators
- Electrocardiographic abnormalities which interfere with ST segment analysis
- False Negatives :

Pacing of right ventricle

1) Earlier myocardial infarction features like Q waves or ST elevation remnant
2) Q waves findings said to be associated with previous MI are ,

a) Q wave in V2-V3≥ 0.02 seconds or QS in V2-V3
b) Q wave ≥ 0.03 seconds and ≥ 0.1mV deep in leads I,II,aVL,aVF
c) In leads I,II,aVL,aVF or V4-V6 when QS complex is seen
d) In V1-V2 R/S ≥1 with positive concordant T wave or R wave ≥ 0.04 seconds in absence of conduction abnormalities

- False positives for STEMI
- Wrong placement of leads while taking ecg
- Pulmonary thromboembolism
- Pericarditis
- Myocarditis
- Subarachnoid hemorrhage
- Electrolyte disturbances like hyperkalemia
- Acute cholecystitis

- Cardiomyopathy
- Transposition of ECG leads
- Patient on drugs like phenothiazines or tricyclic antidepressants

DATA COLLECTION FORM

Name :

Age :

Sex :

Socio economic status : (as per Modified Prasad's classification) Tab.8

SOCIO ECONOMIC CLASS	INCOME PER MONTH PER HEAD
I	>Rs 5571/-
II	Rs 2786-5570/-
III	Rs 1671-2785/-
IV	Rs 836-1670/-
V	< Rs 836/-

Presenting Complaints :

Presenting History :

Past History :

Drug History :

Family History :

Personal History :

General Examination & Vitals :

Systemic Examination : (KILLIP CLASS I TO IV of STEMI patients based on the extent of auscultatory rales as marker for pulmonary edema,S3 and presence or absence of cardiogenic shock- based on cardiovascular and respiratory system examination)

Based on above findings TIMI RISK SCORE for STEMI patients is done in the following manner (useful to assess 30 day mortality-as low risk0-2,and high risk-5-7)1,3.

- Age 65-74 yr/≥75 yr - 2/3 points
- Systolic blood pressure <100mmHg - 3 points
- Heart rate > 100/min - 2 points
- Killip Class II-IV - 2 points
- Anterior STEMI or new LBBB - 1 point
- Diabetes,history of hypertension,history of angina - 1 point
- Weight < 67 kg - 1 point
- Time to treatment <4 hr – 1 point

ECG findings : 3,4

Investigations:

- CBC
- Urine routine
- Serum Creatinine
- Blood Urea
- Serum electrolytes

- TSH
- RBS,HbA1C
- Lipid Profile
- High sensitivity C reactive protein
- Human Heat shock protein 60
- Echocardiographic findings :Ejection fraction, Regional wall motion abnormalities,clot,pericardial effusion,pulmonary arterial hypertension,valvular abnormalities.1,3.
- Percutaneous coronary intervention findings 1,3 : Vessels involved,TIMI 0-3 SCORING based on angiography findings
- TIMI Grade 0 – No blush or minimal blush
- TIMI Grade 1 – Stain present.Blush persists on next injection
- TIMI Grade 2 – Contrast strongly persistent at end of wash out.Gone by next injection
- TIMI Grade 3 – Normal ground glass appearance of blush.Contrast mildly persistent at end of washout

Based on above findings risk factor assessment is done as follows :

I)Non modifiable risk factor

- Age
- Sex
- Family History of CAD/Diabetes mellitus/Systemic Hypertension/Dyslipidemia

II) Modifiable risk factors (as defined in review of literature)

- Obesity & waist hip ratio (WHO 2004)
- Cigarette smoking
- Alcohol consumption
- Psychosocial assessment (Goldberg scale for depression)
- Dietary habits (24 hr recall method)
- Physical Activity(IPAQ questionnaire)
- Diabetes mellitus (ADA 2013 Guidelines)
- Systemic hypertension(JNC 8 Guidelines)
- Dyslipidemia and ASCVD risk score (AHA 2013 Guidelines for Dyslipidemia)

III) Emerging Risk Factors : hs CRP & Human HSP 60

Diet has been calculated as follows,

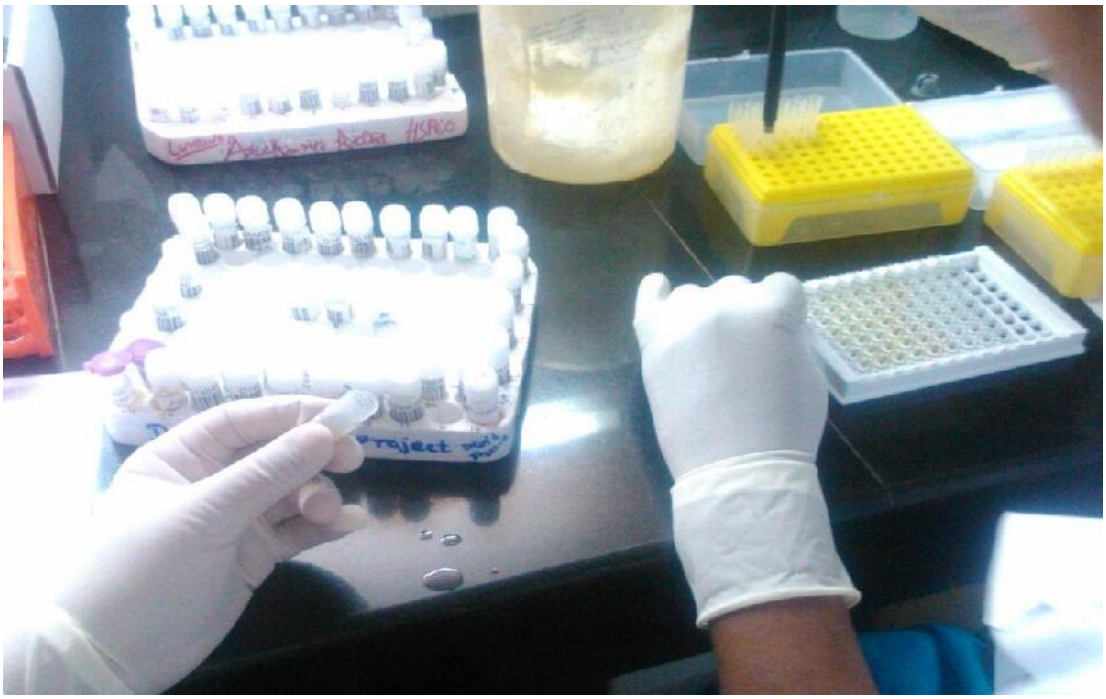
Recommended Dietary Allowance Tab.9

Nutrients	**Man**			**Women**		
	Sedentary	**Moderate**	**Heavy**	**Sedentary**	**Moderate**	**Heavy**
Energy (Kcal)	2425	2875	3800	1875	2225	2925
Protein (g)	60	60	60	50	50	50

Diet history is calculated with 24hr diet recall questionnaire and the told diet history is measured in possible standard measures and converted to calories.Such converted calorie diet is compared with recommended dietary allowance and thus patient is considered to

take high calorie or atherogenic diet when patient has taken diet above their recommended dietary allowance.

Sample collection and Procedure details : Figure 13 & 14



Patient coming to Emergency department with chest pain

↓

Diagnosed as acute coronary syndrome – STEMI

↓

2.5 cc of blood drawn in 0.109 M Sodium citrate

↓

Immediately taken to lab and centrifuged at 3000 x g for ten minutes and plasma is separated

↓

Store -20 for 70 to 80 days and is freeze thawed on day of study

Methodology:

- Microplate wells have to be localised with human HSP 60 standard,2 hours to incubate
- Wash five times with 200 micro litre of wash buffers manually with subsequent decantation and loading
- Add 50 micro litre of biotinylated human HSP 60 antibody and follow 2 hours incubation
- Then add streptividin peroxidase conjugate and incubate at 30 minutes
- Add chromogen 50 microlitre incubate at 30 minutes for blue colour followed by stop solution for yellow colour change
- Read at 450nm of spectrometer and read as the level marked in filter
- Plot a graph with standard concentration on X axis and its absorbance on Y axis
- Sample concentration are obtained from curve and they are multiplied by dilution factor to obtain value
- Values of HSP 60 >2ng/ml are considered to be significant from the test done.
- We ran samples of 33 patients and 27 controls on single day after standardization with standard samples

High sensitivity C reactive protein :

C reactive protein being a acute phase reactant ,which is synthesized in liver and released in conditions related to infection,inflammation and when patients have underlying on going atherosclerosis.However all acute coronary syndrome patients donot have elevated levels of hsCRP.

2.5 ml of blood collected in plain bottle for serum separated from clot immediately and analyzed promptly.Two reagents called R1 and R2 are used, where R1 is TRIS buffer with bovine serum albumin and immunoglobulin and R2 is latex particles coated with anti crp in a glycinated buffer.Sample collected is mixed with reagents and kept in a COBAS integra automatic analyzer,where automatically its calculated and values are obtained.Values >0.5mg/dl are said to be significant.

STATISTICAL ANALYSIS

Case Control Study

- Sample size estimation = 2pq *7.83/d*d
- p is mean of prevalence of cases and controls (p1+p2/2),where p1 and p2 are prevalence of cases and controls respectively
- q=1-p , d=p1-p2
- As per Biasucci LM et al study, hsCRP and Chlamydial HSP 60 were found to be 67% and 30% respectively in ACS patients and normal subjects.56
- Substituting these in the above formula sample size of case and control population is estimated to be 28-30 each.
- Categorical variables were compared using a chi square test, Fisher exact test. The independent variables(risk factors in the study) are compared with the dependent factor(HSP 60 and hs CRP) using multivariate regression analysis and the results are tabulated. All analyses used two sided tests with significance level of p=0.05.Data were analyzed using SPSS version 16.0 for windows (SPSS ,Inc, Chicago, IL,USA)

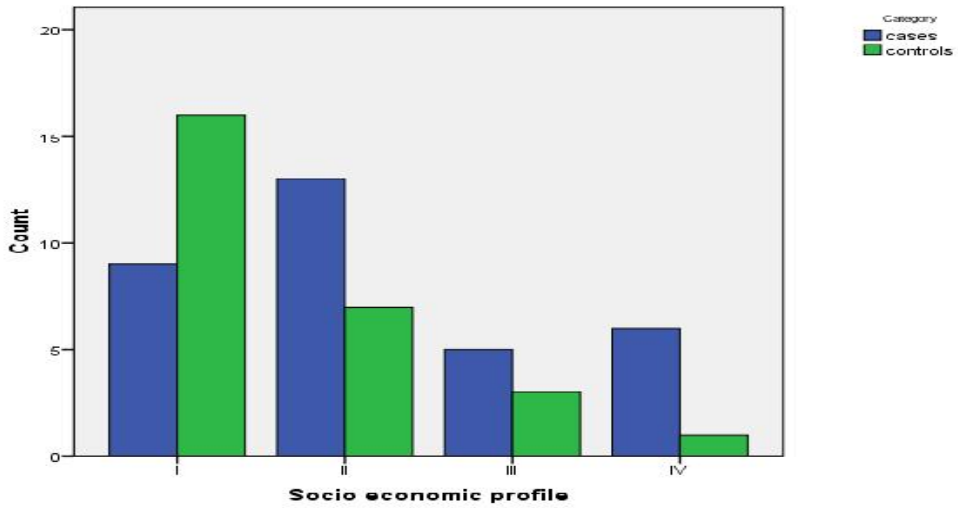
RESULTS

In our study we focused to evaluate the relation of various traditional risk factors with markers of inflammation and infection which are hsCRP and HSP 60.We have analyzed the data in relation with novel risk factors for ACS like inflammation and infection by measuring circulating levels of hsCRP and HSP 60 respectively with possible traditional risk factors.

The traditional risk factors are evaluated are,

1. Type 2 diabetes mellitus
2. Hypertension
3. Dyslipidemia
4. Obesity
5. Diet
6. Physical activity
7. Stress
8. Family History
9. Age
10. 10)Habits

Coming to analysis of socio economic profile rather than as a traditional risk factor we had intended to see the dispersion of various economic strata visiting our hospital. Coming to the analysis of socioeconomic profile, most of the population that is around 72% of them were in II, III, IV economic strata among cases as per modified prasads classification. Among controls 41% were in these classes.



In controls alone : The dispersion and percentages of various data in cases are given as below,

Tab.10-23

Age	Frequency	Percent
18-45	16	59.3
46-80	11	40.7
Total	**27**	**100.0**

Sex	Frequency	Percent
Male	16	59.3
Female	11	40.7
Total	**27**	**100.0**

Hscrp	Frequency	Percent
No	20	74.1
Yes	7	25.9
Total	**27**	**100.0**

HSP 60	Frequency	Percent
No	19	70.4
Yes	8	29.6
Total	**27**	**100.0**

Socio Economic profile	Frequency	Percent
I	16	59.3
II	7	25.9
III	3	11.1
IV	1	3.7
Total	**27**	**100.0**

Physical activity	Frequency	Percent
Inactive	21	77.8
Minimally Inactive	5	18.5
Hepa active	1	3.7
Total	**27**	**100.0**

Diet	Frequency	Percent
As per RDA	12	44.4
More than RDA	11	40.7
Less than RDA	4	14.8
Total	**27**	**100.0**

T2DM	Frequency	Percent
No	22	81.5
Yes	5	18.5
Total	**27**	**100.0**

SHTN	Frequency	Percent
No	25	92.6
Yes	2	7.4
Total	**27**	**100.0**

Dyslipidemia	Frequency	Percent
No	4	14.8
Yes	23	85.2
Total	**27**	**100.0**

Habits	Frequency	Percent
No	18	66.7
Smoker	2	7.4
Alcoholic	5	18.5
Both	2	7.4
Total	**27**	**100.0**

Family history	Frequency	Percent
No	21	77.8
Yes	6	22.2
Total	**27**	**100.0**

Stress	Frequency	Percent
No	12	44.4
Mild	12	44.4
Moderate	2	7.4
Severe	1	3.7
Total	**27**	**100.0**

Obesity	Frequency	Percent
No	9	33.3
Over weight	16	59.3
Obesity	2	7.4
Total	**27**	**100.0**

In cases alone Tab.24-35

Age	Frequency	Percent
18-45	8	24.2
46-80	25	75.8
Total	**33**	**100.0**

Sex	Frequency	Percent
Male	26	78.8
Female	7	21.2
Total	**33**	**10.0**

Physical activity	Frequency	Percent
0	1	3.0
Inactive	26	78.8
Minimally Inactive	6	18.2
Total	**33**	**100.0**

Hscrp	Frequency	Percent
No	15	45.5

Yes	18	54.5
Total	33	100.0

Diet	**Frequency**	**Percent**
As per RDA	12	36.4
More than RDA	15	45.5
Less than RDA	6	18.2
Total	**33**	**100.0**

T2DM	Frequency	Percent
No	14	42.4
Yes	19	57.6
Total	**33**	**100.0**

Hyper Tension	**Frequency**	**Percent**
No	18	70.4
Yes	15	29.6
Total	**33**	**100.0**

Dyslipidemia	Frequency	Percent
Yes	29	87.9
Not known	4	12.1
Total	**33**	**100.0**

Habits	Frequency	Percent
No	13	39.4
Smoker	8	24.2
Alcoholic	2	6.1
Both	10	30.3
Total	**33**	**100.0**

Family history	Frequency	Percent
No	19	57.6
Yes	14	42.4
Total	**33**	**100.0**

Stress	Frequency	Percent
No	5	15.2
Mild	10	30.3
Moderate	11	33.3
Severe	4	12.1
Not known	3	9.1
Total	**33**	**100.0**

Obesity	**Frequency**	**Percent**
No	5	15.2
Over weight	16	48.5
Obesity	12	36.4
Total	**33**	**100.0**

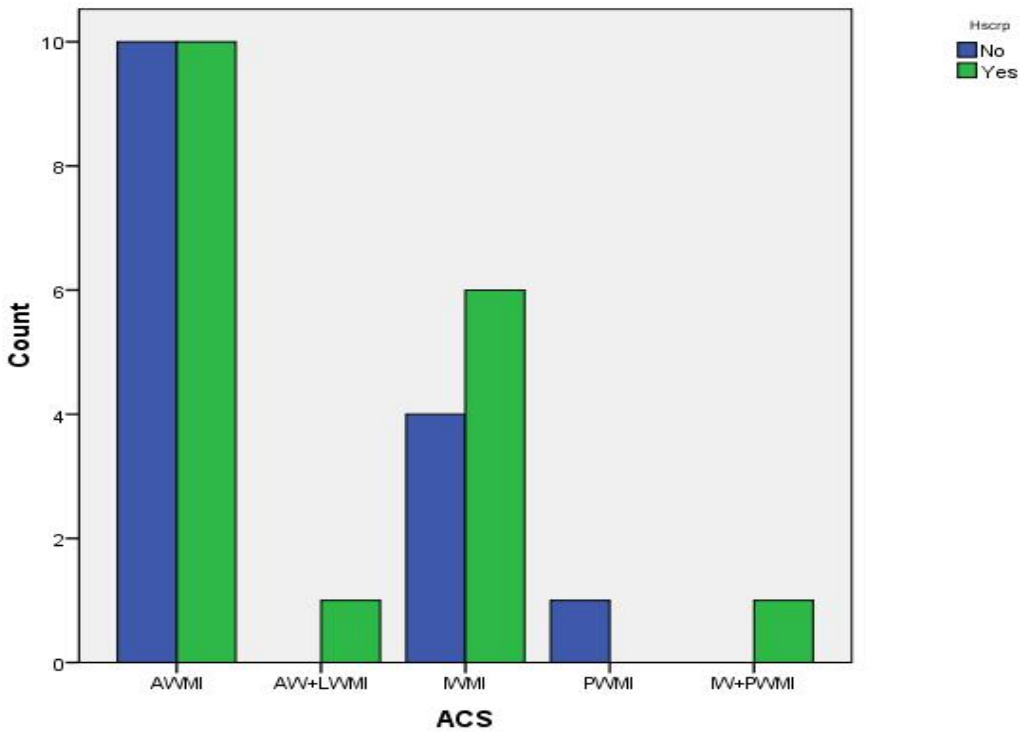
Among cases with STEMI the following is the incidence of various mi, with anterior wall mi being highest in occurrence with 60.6% and clinically Killip class I/II were 42.2 and 45.5 %. **Tab.25-26**

ACS	**Frequency**	**Percent**
AWMI	20	60.6
AW+LWMI	1	3.0
IWMI	10	30.3
PWMI	1	3.0
IW+PWMI	1	3.0
Total	**33**	**100.0**

Killip Class	Frequency	Percent
CLASS I	14	42.4
CLASS II	15	45.5
CLASS III	2	6.1
CLASS IV	2	6.1
Total	**33**	**100.0**

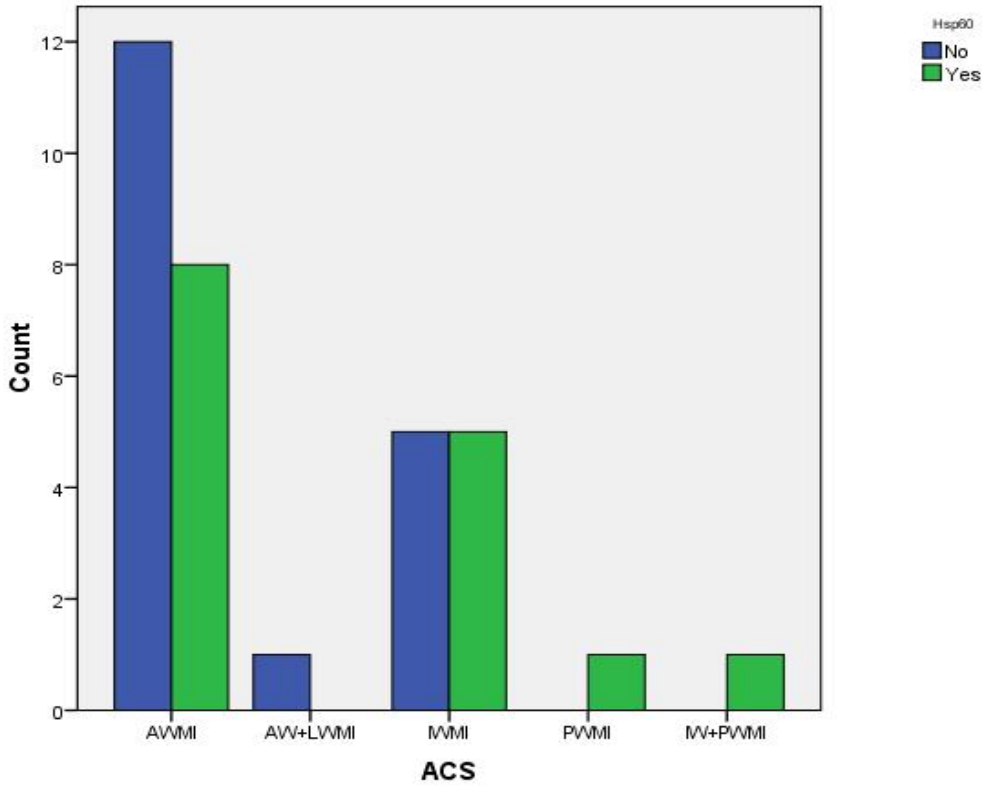
Comparision between hsCRP and type of MI **Tab.27**

			Hscrp			
			No	**Yes**	**Total**	**P value**
ACS	AWMI	No	10	10	20	0.533
		%	66.7%	55.6%	60.6%	
	AW+LWMI	No	0	1	1	
		%	.0%	5.6%	3.0%	
	IWMI	No	4	6	10	
		%	26.7%	33.3%	30.3%	
	PWMI	No	1	0	1	
		%	6.7%	.0%	3.0%	
	IW+PWMI	No	0	1	1	
		%	.0%	5.6%	3.0%	
Total		**No**	**15**	**18**	**33**	
		%	**100.0%**	**100.0%**	**100.0%**	



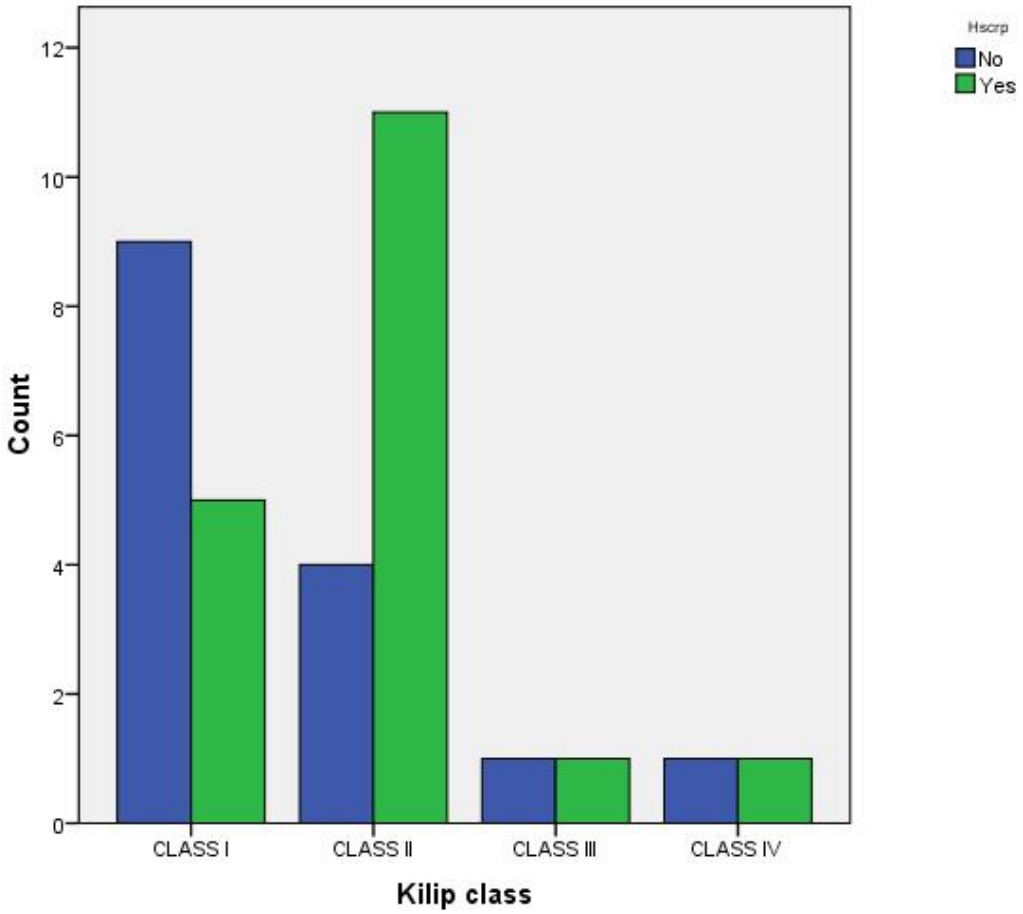
Comparision between type of wall involvement and HSP 60 values **Tab.28**

			Hsp60			
			No	**Yes**	**Total**	**P value**
ACS	AWMI	No	12	8	20	0.469
		%	66.7%	53.3%	60.6%	
	AW+LWMI	No	1	0	1	
		%	5.6%	.0%	3.0%	
	IWMI	No	5	5	10	
		%	27.8%	33.3%	30.3%	
	PWMI	No	0	1	1	
		%	.0%	6.7%	3.0%	
	IW+PWMI	No	0	1	1	
		%	.0%	6.7%	3.0%	
Total		**No**	**18**	**15**	**33**	
		%	**100.0%**	**100.0%**	**100.0%**	



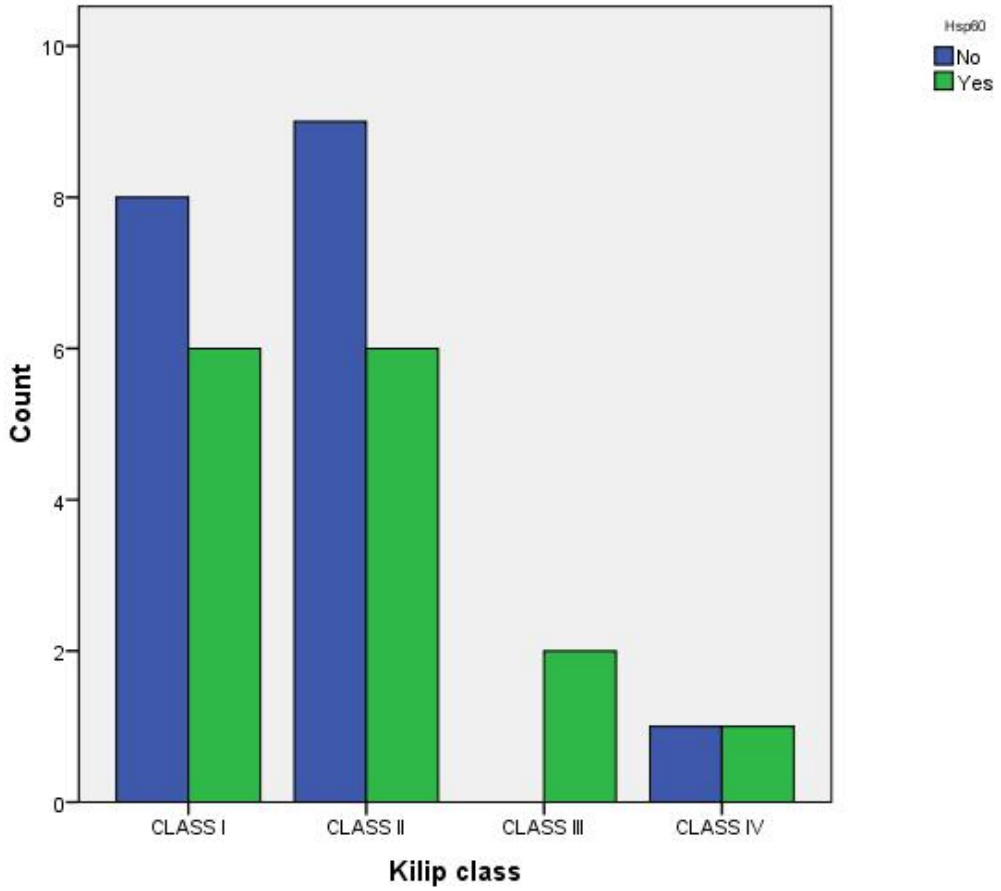
Comparison between HSCRP & Killip class in cases alone **Tab.29**

			Hscrp			
			No	**Yes**	**Total**	**P value**
Kilip class	CLASS I	No	9	5	14	0.244
		%	60.0%	27.8%	42.4%	
	CLASS II	No	4	11	15	
		%	26.7%	61.1%	45.5%	
	CLASS III	No	1	1	2	
		%	6.7%	5.6%	6.1%	
	CLASS IV	No	1	1	2	
		%	6.7%	5.6%	6.1%	
Total		**No**	**15**	**18**	**33**	
		%	**100.0%**	**100.0%**	**100.0%**	



Comparison between HSP60 & Killip class in cases alone **Tab.30**

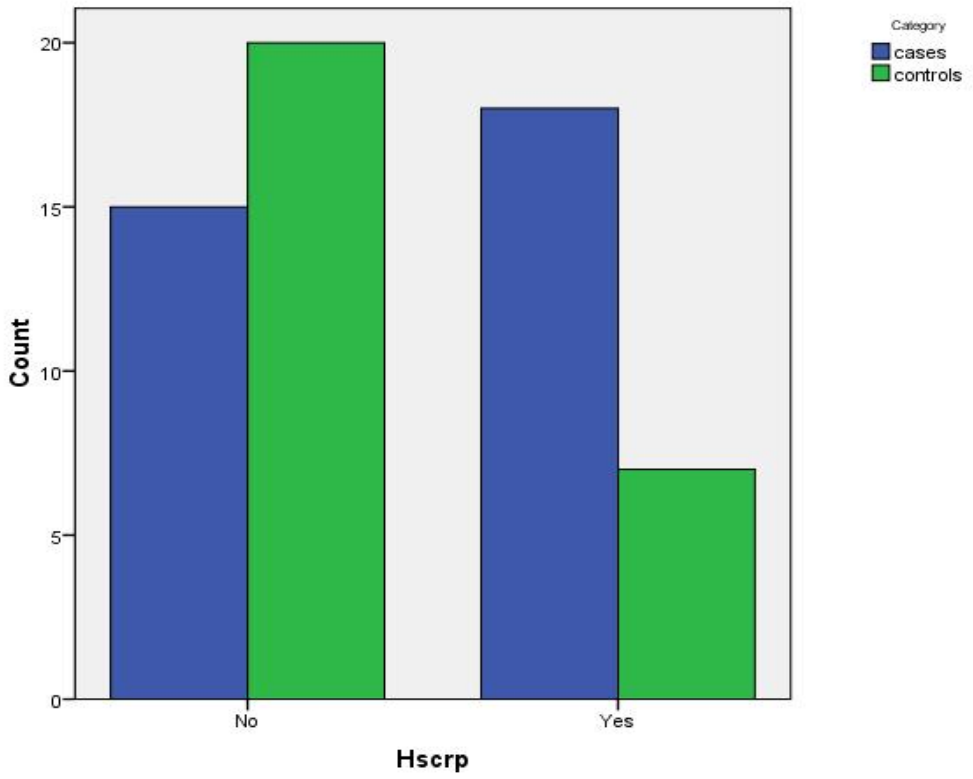
			Hsp60			
			No	**Yes**	**Total**	**P value**
Kilip class	CLASS I	No	8	6	14	0.451
		%	44.4%	40.0%	42.4%	
	CLASS II	No	9	6	15	
		%	50.0%	40.0%	45.5%	
	CLASS III	No	0	2	2	
		%	.0%	13.3%	6.1%	
	CLASS IV	No	1	1	2	
		%	5.6%	6.7%	6.1%	
Total		**No**	**18**	**15**	**33**	
		%	**100.0%**	**100.0%**	**100.0%**	



The levels of HSCRP were positive in 54.5% of cases and 25.9% of controls. While the levels were absent or not detectable that is value was less than 0.5 mg/dl (as per our lab reference) in 74.1% of controls and45.5% of cases. When assessed for statistical significance, it was found that the p value for HSCRP was found to be <0.05 with a value of 0.023. It signifies that the level of HSCRP was statistically significant in cases. The ODDs ratio was 3.43, with CI not spanning much, indicating its significance on outcome of acute coronary syndrome. The levels of HSP60 in the cases and controls were significant (.2mg/ml) in 29.6% and 29.6% respectively. When evaluated for statistical significance, there was found to be no statistical significant p value (0.162). However, the ODDs ratio is 1.54 indicating the possibility or ODDs of relation with exposure to infection having relation with acute coronary syndrome outcome. The CI is

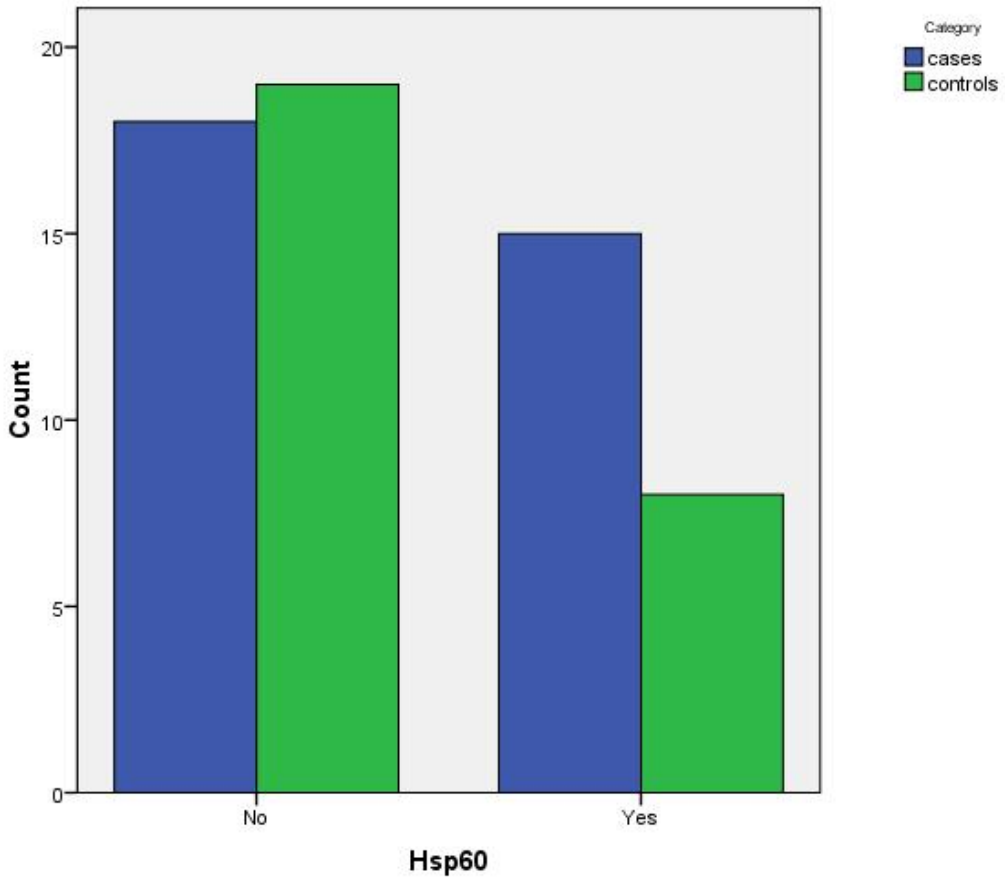
spanned between 1.478 and 0.173 with wide range signifying losses, possibility of relation or risk of infection causing ACS, 30.3% of cases had both positive values of HSP60 and hSCRP while 11.1% had both positive values. The p value for both being 0.068. However among the four cases who died three had both positive values for hSCRP and HSP60. **Tab.31**

			Cases or Controls			
			Cases	**Controls**	**Total**	**P value**
HSCRP	No	No	15	20	35	0.023
		%	45.5%	74.1%	58.3%	
	Yes	No	18	7	25	
		%	54.5%	25.9%	41.7%	
Total		**No**	**33**	**27**	**60**	
		%	**100.0%**	**100.0%**	**100.0%**	



Tab.32

			Cases or Controls			
			Cases	**Controls**	Total	**P value**
HSP 60	No	No	**18**	**19**	**37**	**0.162**
		%	54.5%	70.4%	61.7%	
	Yes	No	15	8	23	
		%	45.5%	29.6%	38.3%	
Total		**No**	**33**	**27**	**60**	
		%	**100.0%**	**100.0%**	**100.0%**	



20 of 33 patients had anterior wall MI and 10 of 33 patients had inferior wall MI and one had lateral wall and two had posterior wall MI along with inferior wall MI. Of

these 10 who had inferior wall MI 4 had both hsCRP and HSP 60 positive while among 20 anterior wall MI 5 had both positive.HSP 60 was positive in 8 of 20 anterior wall MI and 5 of 10 inferior wall MI. Level of inflammation was also relatively more often seen in inferior wall MI patients. Of these 12 had complications secondary to ACS, most common being MR and followed by cardiogenic shock and VT,VF.MR is commonly seen associated with inferior wall MI.

Of 33 patients 7 have been thrombolysed in hospital and 4 have been thrombolysed outside with one failed lysis. Among these patients who have been thrombolysed outside and referred for complications had elevated hsCRP compared to in hospital thrombolysed patients.

Of 33 patients 22 underwent PCI, where 7 underwent primary PCI with drug eluting stent placement. Among these two had restenoses of stent within a duration of a week and both these patients are associated with significantly elevated values of hsCRP and HSP 60.Among 4 cases which expired 3 of them had both hsCRP and HSP 60 values elevation, of them one had hepatitis B infection. However 2 patients had lower respiratory tract infection during hospital stay and they did not have much elevation of HSP 60 compared to hepatitis B patient suggesting role of HSP 60 in chronic infection. This needs further evaluation.

Of the 22 patients who underwent PCI 9 had triple vessel disease. Among the 9 patients 3 had both elevated hsCRP and HSP 60 while 2 had hsCRP alone elevated. Patients with single and double vessel disease were 11 and among them 4 had elevation of both hsCRP and HSP 60 while HSP 60 and hsCRP were individually elevated in 2 each of these patients.

Among these patients ,3 got discharged against medical advise even prior to admission while 4 were dead during hospital stay 3 due to cardiac arrest secondary to VT,VF and one due to restenoses of stent.The remaining 26 patients 13 were under follow up and the other 13 are yet to come for follow up.

Comparisons of all risk factors with HSCRP :

For traditional risk factors the statistical analysis is as follows,

Tab.33

TD2M				Hscrp		Total	P value
				No	Yes		
No	Category	With ACS & Killip Class	Count	9	5	14	0.318
			% within Hscrp	34.6%	50.0%	38.9%	
		Without ACS& Killip Class	Count	17	5	22	
			% within Hscrp	65.4%	50.0%	61.1%	
	Total		**Count**	**26**	**10**	**36**	
			% within Hscrp	**100.0%**	**100.0%**	**100.0%**	
Yes	Category	With ACS & Killip Class	Count	6	13	19	0.255
			% within Hscrp	66.7%	86.7%	79.2%	
		Without ACS & Killip Class	Count	3	2	5	
			% within Hscrp	33.3%	13.3%	20.8%	
	Total		**Count**	**9**	**15**	**24**	
			% within Hscrp	**100.0%**	**100.0%**	**100.0%**	

The age old known risk factors as type 2 diabetes mellitus is present in 57.6% of cases and 18.5% of controls. Diabetics seems to have statistical significant influence on the level of hsCRP ,with a p value of 0.002.However like habits, diabetes when compared in both case and controls to the level of inflammation donot seem to have a statistical significance.

Tab.34

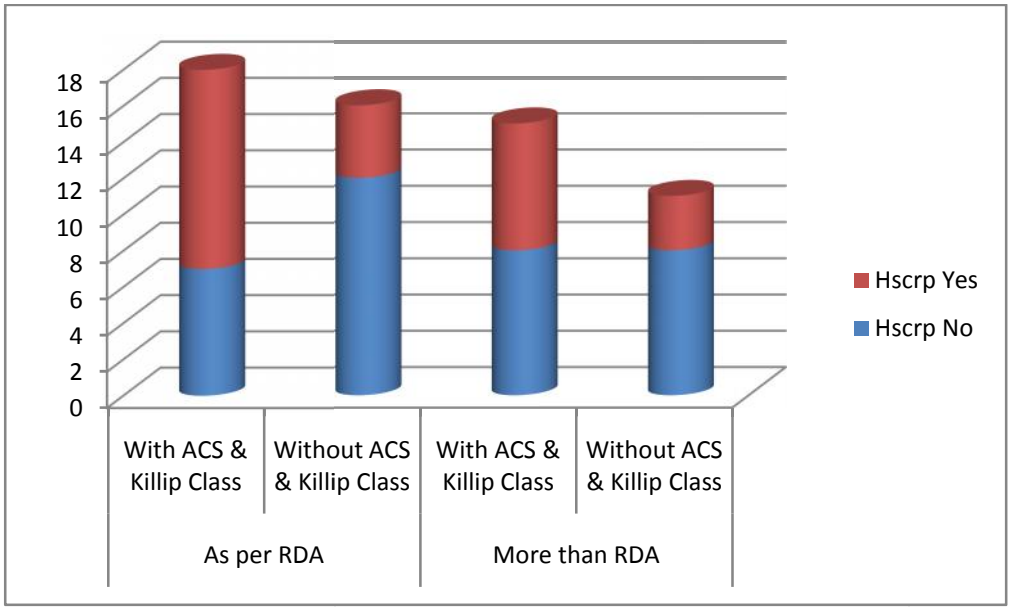
Physical activity				Hscrp		Total	P value
				No	Yes		
0	Category	With ACS & Killip Class	Count	1		1	
			% within Hscrp	100.0%		100.0%	
	Total		**Count**	**1**		**1**	
			% within Hscrp	**100.0%**		**100.0%**	
Inactive	Category	With ACS & Killip Class	Count	14	18	32	0.034
			% within Hscrp	42.4%	72.0%	55.2%	
		Without ACS & Killip Class	Count	19	7	26	
			% within Hscrp	57.6%	28.0%	44.8%	
	Total		**Count**	**33**	**25**	**58**	
			% within Hscrp	**100.0%**	**100.0%**	**100.0%**	
Hepa active	Category	Without ACS & Killip Class	Count	1		1	
			% within Hscrp	100.0%		100.0%	
	Total		**Count**	**1**		**1**	
			% within Hscrp	**100.0%**		**100.0%**	

Physical activity as per IPAQ question questionnaire analysis was done and patients with physical inactivity had more incidences of ACS and relation with hSCRP was statistically significant with P value of 0.034.

More calorie diet as per 24 hour diet recall and following RDA guidelines for Indian population gave an outcome of 55% of cases having such diet. On comparing with hsCRP it does not have a statistical significance in patients and controls with elevated hsCRP while there was surprisingly relation between low calorie or normal diet in cases and controls with elevation of hsCRP.

Tab.35

Diet				Hscrp		Total	P value
				No	Yes		
As per RDA	Category	With ACS & Killip Class	Count	7	11	18	0.037
			% within Hscrp	36.8%	73.3%	52.9%	
		Without ACS & Killip Class	Count	12	4	16	
			% within Hscrp	63.2%	26.7%	47.1%	
	Total		**Count**	**19**	**15**	**34**	
			% within Hscrp	**100.0%**	**100.0%**	**100.0%**	
More than RDA	Category	With ACS & Killip Class	Count	8	7	15	0.277
			% within Hscrp	50.0%	70.0%	57.7%	
		Without ACS & Killip Class	Count	8	3	11	
			% within Hscrp	50.0%	30.0%	42.3%	
	Total		**Count**	**16**	**10**	**26**	
			% within Hscrp	**100.0%**	**100.0%**	**100.0%**	



The influence of systemic hypertension neither seem to have statistical significance in cases or controls with hsCRP and overall together in entire study population.

Tab.36

SHTN				Hscrp		Total	P value
				No	Yes		
No	Category	With ACS & Killip Class	Count	8	8	16	0.085
			% within Hscrp	29.6%	57.1%	39.0%	
		Without ACS & Killip Class	Count	19	6	25	
			% within Hscrp	70.4%	42.9%	61.0%	
	Total		**Count**	**27**	**14**	**41**	
			% within Hscrp	**100.0%**	**100.0%**	**100.0%**	
Yes	Category	With ACS & Killip Class	Count	7	10	17	0.678
			% within Hscrp	87.5%	90.9%	89.5%	
		Without ACS & Killip Class	Count	1	1	2	
			% within Hscrp	12.5%	9.1%	10.5%	
	Total		**Count**	**8**	**11**	**19**	
			% within Hscrp	**100.0%**	**100.0%**	**100.0%**	

Dyslipidemia ,seem to have a significant statistical significance in cases and influence to level of inflammation in body with a p value of 0.017.

In overall study population too,the level of dyslipidemia seen in 87.9% cases and 85.2% of controls seem to have a statistical significant p value of 0.015.

Tab.37

Dyslipidemia				Hscrp		Total	P value
				No	Yes		
No	Category	Without ACS & Killip Class	Count	2	2	4	
			% within Hscrp	100.0%	100.0%	100.0%	
	Total		**Count**	**2**	**2**	**4**	
			% within Hscrp	**100.0%**	**100.0%**	**100.0%**	
Yes	Category	With ACS & Killip Class	Count	13	16	29	0.015
			% within Hscrp	41.9%	76.2%	55.8%	
		Without ACS & Killip Class	Count	18	5	23	
			% within Hscrp	58.1%	23.8%	44.2%	
	Total		**Count**	**31**	**21**	**52**	
			% within Hscrp	**100.0%**	**100.0%**	**100.0%**	
2	Category	With ACS & Killip Class	Count	2	2	4	
			% within Hscrp	100.0%	100.0%	100.0%	
	Total		**Count**	**2**	**2**	**4**	
			% within Hscrp	**100.0%**	**100.0%**	**100.0%**	

Presence of habits seem to have statistical significance in cases with relation to hs CRP where p value is 0.015.Habits include smoking, alcohol intake and both. Among cases both smoking and alcoholic patients are 33.3% and alcoholic and smokers alone are 6.1% and 24.2% respectively. Among controls, more percentage that is 66.7% donot have any habits. However ,seen overall, habits donot seem to influence the level of hsCRP in the cases and controls.

Tab.38

Habits				Hscrp		Total	P value
				No	Yes		
No	Category	With ACS & Killip Class	Count	5	8	13	0.065
			% within Hscrp	27.8%	61.5%	41.9%	
		Without ACS & Killip Class	Count	13	5	18	
			% within Hscrp	72.2%	38.5%	58.1%	
	Total		**Count**	**18**	**13**	**31**	
			% within Hscrp	**100.0%**	**100.0%**	**100.0%**	
Smoker	Category	With ACS & Killip Class	Count	3	5	8	0.667
			% within Hscrp	75.0%	83.3%	80.0%	
		Without ACS & Killip Class	Count	1	1	2	
			% within Hscrp	25.0%	16.7%	20.0%	
	Total		**Count**	**4**	**6**	**10**	
			% within Hscrp	**100.0%**	**100.0%**	**100.0%**	
Alcoholic	Category	With ACS & Killip Class	Count	2	0	2	0.714
			% within Hscrp	33.3%	.0%	28.6%	
		Without ACS & Killip Class	Count	4	1	5	
			% within Hscrp	66.7%	100.0%	71.4%	
	Total		**Count**	**6**	**1**	**7**	
			% within Hscrp	**100.0%**	**100.0%**	**100.0%**	
Both	Category	With ACS & Killip Class	Count	5	5	10	0.318
			% within Hscrp	71.4%	100.0%	83.3%	
		Without ACS & Killip Class	Count	2	0	2	
			% within Hscrp	28.6%	.0%	16.7%	
	Total		**Count**	**7**	**5**	**12**	
			% within Hscrp	**100.0%**	**100.0%**	**100.0%**	

In case of family history too there was statistical significance in population without family history of acute coronary syndrome in relation to hsCRP values with a significant p value of 0.013.Overall 14 cases had family history of CAD and 6 controls had family history of coronary artery disease.

Tab.39

Family History				Hscrp		Total	P value
				No	Yes		
No	Category	With ACS & Killip Class	Count	8	11	19	0.013
			% within Hscrp	32.0%	73.3%	47.5%	
		Without ACS & Killip Class	Count	17	4	21	
			% within Hscrp	68.0%	26.7%	52.5%	
	Total		**Count**	**25**	**15**	**40**	
			% within Hscrp	**100.0%**	**100.0%**	**100.0%**	
Yes	Category	With ACS & Killip Class	Count	7	7	14	0.686
			% within Hscrp	70.0%	70.0%	70.0%	
		Without ACS & Killip Class	Count	3	3	6	
			% within Hscrp	30.0%	30.0%	30.0%	
	Total		**Count**	**10**	**10**	**20**	
			% within Hscrp	**100.0%**	**100.0%**	**100.0%**	

Stress levels as assessed by Goldberg Depression scale revealed only 75% of the patients had no stress while rest had stress in various categories ranging from mild, moderate to severe. However due to acute presentation and death within few hours of admission among 3 cases, stress levels with questionnaire form could not be assessed. Among controls without stress were almost 40%. However, no statistical significance was found between various gradings of stress and hsCRP levels.

Tab.40

Stress				Hscrp		Total	P value
				No	Yes		
No	Category	With ACS & Killip Class	Count	3	2	5	0.330
			% within Hscrp	23.1%	50.0%	29.4%	
		Without ACS & Killip Class	Count	10	2	12	
			% within Hscrp	76.9%	50.0%	70.6%	
	Total		**Count**	**13**	**4**	**17**	
			% within Hscrp	**100.0%**	**100.0%**	**100.0%**	
Mild	Category	With ACS & Killip Class	Count	4	6	10	0.335
			% within Hscrp	36.4%	54.5%	45.5%	
		Without ACS & Killip Class	Count	7	5	12	
			% within Hscrp	63.6%	45.5%	54.5%	
	Total		**Count**	**11**	**11**	**22**	
			% within Hscrp	**100.0%**	**100.0%**	**100.0%**	
Moderate	Category	With ACS & Killip Class	Count	5	6	11	0.269
			% within Hscrp	71.4%	100.0%	84.6%	
		Without ACS & Killip Class	Count	2	0	2	
			% within Hscrp	28.6%	.0%	15.4%	
	Total		**Count**	**7**	**6**	**13**	
			% within Hscrp	**100.0%**	**100.0%**	**100.0%**	
Severe	Category	With ACS & Killip Class	Count	1	3	4	0.400
			% within Hscrp	50.0%	100.0%	80.0%	
		Without ACS & Killip Class	Count	1	0	1	
			% within Hscrp	50.0%	.0%	20.0%	
	Total		**Count**	**2**	**3**	**5**	
			% within Hscrp	**100.0%**	**100.0%**	**100.0%**	
Not known	Category	With ACS & Killip Class	Count	2	1	3	
			% within Hscrp	100.0%	100.0%	100.0%	
	Total		**Count**	**2**	**1**	**3**	
			% within Hscrp	**100.0%**	**100.0%**	**100.0%**	

Obesity as graded by WHO criteria showed 84.8% of cases in overweight and obesity cader and 66.66% of controls with obesity. Similarly they also seem to influence the hsCRP values. **Tab.41**

Obesity				Hscrp		Total	P value
				No	Yes		
No	Category	With ACS & Killip Class	Count	1	4	5	0.023
			% within Hscrp	11.1%	80.0%	35.7%	
		Without ACS & Killip Class	Count	8	1	9	
			% within Hscrp	88.9%	20.0%	64.3%	
	Total		**Count**	**9**	**5**	**14**	
			% within Hscrp	**100.0%**	**100.0%**	**100.0%**	
Over weight	Category	With ACS & Killip Class	Count	14	14	28	0.210
			% within Hscrp	53.8%	70.0%	60.9%	
		Without ACS & Killip Class	Count	12	6	18	
			% within Hscrp	46.2%	30.0%	39.1%	
	Total		**Count**	**26**	**20**	**46**	
			% within Hscrp	**100.0%**	**100.0%**	**100.0%**	

Tab.42

Age				Hscrp		Total	P value
				No	Yes		
18-45	Category	With ACS & Killip Class	Count	5	3	8	0.302
			% within Hscrp	27.8%	50.0%	33.3%	
		Without ACS & Killip Class	Count	13	3	16	
			% within Hscrp	72.2%	50.0%	66.7%	
	Total		**Count**	**18**	**6**	**24**	
			% within Hscrp	**100.0%**	**100.0%**	**100.0%**	
46-80	Category	With ACS & Killip Class	Count	10	15	25	0.172
			% within Hscrp	58.8%	78.9%	69.4%	
		Without ACS & Killip Class	Count	7	4	11	
			% within Hscrp	41.2%	21.1%	30.6%	
	Total		**Count**	**17**	**19**	**36**	
			% within Hscrp	**100.0%**	**100.0%**	**100.0%**	

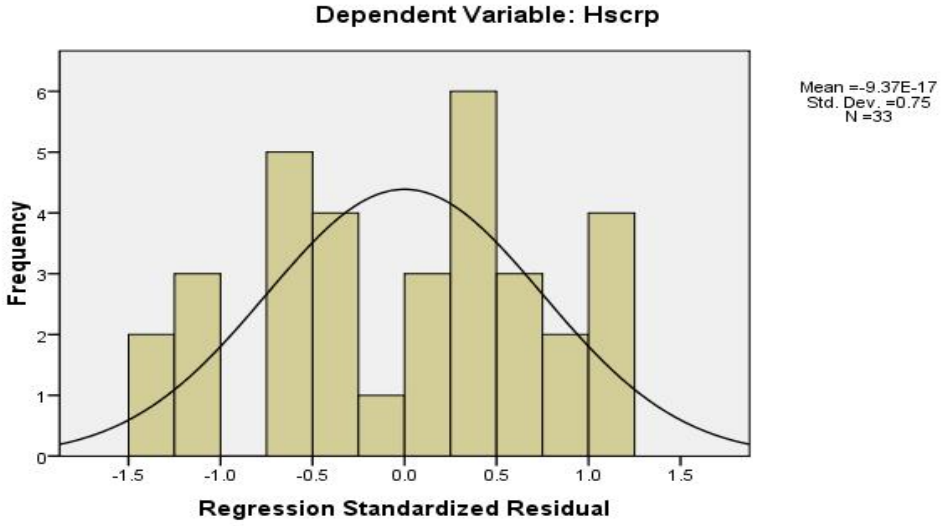
Regression analysis for hsCRP AS DEPENDENT VARIABLE

Model Summary[b]					
Model	**R**	**R Square**	**Adjusted R Square**	**Std. Error of the Estimate**	**Overall significance**
1	.756[a]	.571	.237	.44155	0.141
a. Predictors: (Constant), Killip class, Physical activity, Diet, age, ACS, Obesity, TD2M, Socio economic profile, Family History, SHTN, Stress, sex, Habits, Dyslipidemia					
b. Dependent Variable: Hscrp					

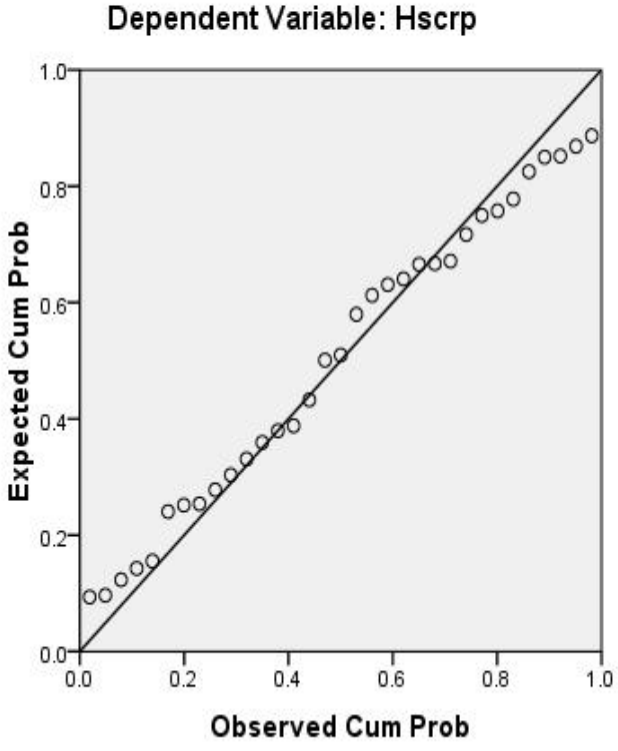
Tab.43

Coefficients[a]						
Model		**Unstandardized Coefficients**		**Standardized Coefficients**	**T**	**Sig.**
		B	**Std. Error**	**Beta**		
1	(Constant)	1.699	.730		2.329	.032
	Age	.323	.246	.278	1.311	.206
	Sex	-.364	.277	-.299	-1.315	.205
	Socio economic profile	.132	.096	.277	1.376	.186
	Physical activity	-.584	.257	-.510	-2.269	.036
	Diet	-.146	.149	-.210	-.978	.341
	TD2M	.345	.180	.343	1.917	.071
	SHTN	-.165	.213	-.165	-.774	.449
	Dyslipidemia	-.823	.443	-.539	-1.857	.080
	Habits	-.113	.088	-.287	-1.279	.217
	Family History	-.291	.196	-.289	-1.487	.154
	Stress	-.035	.122	-.080	-.287	.777
	Obesity	-.246	.135	-.339	-1.825	.085
	ACS	-.018	.096	-.040	-.184	.856
		.364	.156	.598	2.329	.032
a. Dependent Variable: Hscrp						

Histogram



Normal P-P Plot of Regression Standardized Residual



COMPARISION OF HSP 60 WITH TRADITIONAL RISK FACTORS

Tab.44

Physical activity				Hsp60		Total	P value
				No	Yes		
0	Category	With ACS & Killip class	Count	1		1	
			% within Hsp60	100.0%		100.0%	
	Total		**Count**	**1**		**1**	
			% within Hsp60	**100.0%**		**100.0%**	
Inactive	Category	With ACS & Killip class	Count	17	15	32	0.164
			% within Hsp60	48.6%	65.2%	55.2%	
		Without ACS & killip class	Count	18	8	26	
			% within Hsp60	51.4%	34.8%	44.8%	
	Total		**Count**	**35**	**23**	**58**	
			% within Hsp60	**100.0%**	**100.0%**	**100.0%**	
Hepa active	Category	Without ACS & killip class	Count	1		1	
			% within Hsp60	100.0%		100.0%	
	Total		**Count**	**1**		**1**	
			% within Hsp60	**100.0%**		**100.0%**	

This explains the distribution of physical activity in cases and controls and their relation with HSP 60 values. Most of the population in the study seem to be physically inactive.

Tab.45

Diet				Hsp60		Total	P value
				No	Yes		
As per RDA	Category	With ACS & Killip class	**Count**	**11**	**7**	**18**	0.459
			% within Hsp60	50.0%	58.3%	52.9%	
		Without ACS & killip class	Count	11	5	16	
			% within Hsp60	50.0%	41.7%	47.1%	
	Total		**Count**	**22**	**12**	**34**	
			% within Hsp60	**100.0%**	**100.0%**	**100.0%**	
More than RDA	Category	With ACS & Killip class	Count	7	8	15	0.178
			% within Hsp60	46.7%	72.7%	57.7%	
		Without ACS & kilip class	Count	8	3	11	
			% within Hsp60	53.3%	27.3%	42.3%	
	Total		**Count**	**15**	**11**	**26**	
			% within Hsp60	**100.0%**	**100.0%**	**100.0%**	

This table highlights the fact that most of the population are taking food above RDA guidelines and their distribution on comparision with HSP 60 VALUES.HSP 60 does not seem to have statistical significance with diet.

Tab.46

TD2M				Hsp60		Total	P value
				No	Yes		
No	Category	With ACS & Killip class	Count	6	8	14	0.075
			% within Hsp60	27.3%	57.1%	38.9%	
		Without ACS & killip class	Count	16	6	22	
			% within Hsp60	72.7%	42.9%	61.1%	
	Total		**Count**	**22**	**14**	**36**	
			% within Hsp60	**100.0%**	**100.0%**	**100.0%**	
Yes	Category	With ACS & Killip class	Count	12	7	19	0.640
			% within Hsp60	80.0%	77.8%	79.2%	
		Without ACS & killip class	Count	3	2	5	
			% within Hsp60	20.0%	22.2%	20.8%	
	Total		**Count**	**15**	**9**	**24**	
			% within Hsp60	**100.0%**	**100.0%**	**100.0%**	

This table highlights the fact that absence of diabetes has statistical significance in the levels of HSP60 in both cases and controls.

Tab.47

SHTN				Hsp60		Total	P value
				No	Yes		
No	Category	With ACS & Killip class	Count	8	8	16	0.137
			% within Hsp60	30.8%	53.3%	39.0%	
		Without ACS & killip class	Count	18	7	25	
			% within Hsp60	69.2%	46.7%	61.0%	
	Total		**Count**	**26**	**15**	**41**	
			% within Hsp60	**100.0%**	**100.0%**	**100.0%**	
Yes	Category	With ACS & Killip class	Count	10	7	17	0.678
			% within Hsp60	90.9%	87.5%	89.5%	
		Without ACS & killip class	Count	1	1	2	
			% within Hsp60	9.1%	12.5%	10.5%	
	Total		**Count**	**11**	**8**	**19**	
			% within Hsp60	**100.0%**	**100.0%**	**100.0%**	

This table explains that either absence or presence of hypertension has no influence on HSP 60 values

Tab.48

Dyslipidemia				Hsp60		Total	
				No	Yes		P value
No	Category	Without ACS & kilip class	Count	3	1	4	
			% within Hsp60	100.0%	100.0%	100.0%	
	Total		**Count**	**3**	**1**	**4**	
			% within Hsp60	**100.0%**	**100.0%**	**100.0%**	
Yes	Category	With ACS & Killip class	Count	15	14	29	0.154
			% within Hsp60	48.4%	66.7%	55.8%	
		Without ACS & killip class	Count	16	7	23	
			% within Hsp60	51.6%	33.3%	44.2%	
	Total		**Count**	**31**	**21**	**52**	
			% within Hsp60	**100.0%**	**100.0%**	**100.0%**	
2	Category	With ACS & Killip class	Count	3	1	4	
			% within Hsp60	100.0%	100.0%	100.0%	
	Total		**Count**	**3**	**1**	**4**	
			% within Hsp60	**100.0%**	**100.0%**	**100.0%**	

Tab.49

Habits				Hsp60		Total	P value
				No	Yes		
No	Category	With ACS & Killip class	Count	8	5	13	0.534
			% within Hsp60	40.0%	45.5%	41.9%	
		Without ACS & killip class	Count	12	6	18	
			% within Hsp60	60.0%	54.5%	58.1%	
	Total		Count	20	11	31	
			% within Hsp60	100.0%	100.0%	100.0%	
Smoker	Category	With ACS & Killip class	Count	5	3	8	0.667
			% within Hsp60	83.3%	75.0%	80.0%	
		Without ACS & kilip class	Count	1	1	2	
			% within Hsp60	16.7%	25.0%	20.0%	
	Total		**Count**	**6**	**4**	**10**	
			% within Hsp60	**100.0%**	**100.0%**	**100.0%**	
Alcoholic	Category	With ACS & Killip class	Count	0	2	2	0.143
			% within Hsp60	.0%	66.7%	28.6%	
		Without ACS & killip class	Count	4	1	5	
			% within Hsp60	100.0%	33.3%	71.4%	
	Total		**Count**	**4**	**3**	**7**	
			% within Hsp60	**100.0%**	**100.0%**	**100.0%**	
Both	Category	With ACS & Killip class	Count	5	5	10	0.318
			% within Hsp60	71.4%	100.0%	83.3%	
		Without ACS & killip class	Count	2	0	2	
			% within Hsp60	28.6%	.0%	16.7%	
	Total		**Count**	**7**	**5**	**12**	
			% within Hsp60	**100.0%**	**100.0%**	**100.0%**	

Tab.50

Family History				Hsp60		Total	
				No	Yes		P value
No	Category	With ACS & Killip class	Count	9	10	19	0.273
			% within Hsp60	40.9%	55.6%	47.5%	
		Without ACS & killip class	Count	13	8	21	
			% within Hsp60	59.1%	44.4%	52.5%	
	Total		**Count**	**22**	**18**	**40**	
			% within Hsp60	**100.0%**	**100.0%**	**100.0%**	
Yes	Category	With ACS & Killip class	Count	9	5	14	0.129
			% within Hsp60	60.0%	100.0%	70.0%	
		Without ACS & killip class	Count	6	0	6	
			% within Hsp60	40.0%	.0%	30.0%	
	Total		**Count**	**15**	**5**	**20**	
			% within Hsp60	**100.0%**	**100.0%**	**100.0%**	

Tab.51 & 52

Stress				Hsp60		Total	P value
				No	Yes		
No	Category	With ACS & Killip class	Count	3	2	5	0.472
			% within Hsp60	25.0 %	40.0%	29.4%	
		Without ACS & killip class	Count	9	3	12	
			% within Hsp60	75.0 %	60.0%	70.6%	
	Total		**Count**	**12**	**5**	**17**	
			% within Hsp60	**100.0 %**	**100.0%**	**100.0%**	
Mild	Category	With ACS & Killip class	Count	6	4	10	0.639
			% within Hsp60	46.2 %	44.4%	45.5%	
		Without ACS & killip class	Count	7	5	12	
			% within Hsp60	53.8 %	55.6%	54.5%	
	Total		**Count**	**13**	**9**	**22**	
			% within Hsp60	**100.0 %**	**100.0%**	**100.0%**	
Moderate	Category	With ACS & Killip class	Count	4	7	11	0.192
			% within Hsp60	66.7 %	100.0%	84.6%	
		Without ACS & killip class	Count	2	0	2	
			% within Hsp60	33.3 %	.0%	15.4%	
	Total		**Count**	**6**	**7**	**13**	
			% within Hsp60	**100.0 %**	**100.0%**	**100.0%**	
Severe	Category	With ACS & Killip class	Count	2	2	4	0.600
			% within Hsp60	66.7 %	100.0%	80.0%	
		Without ACS & killip class	Count	1	0	1	
			% within Hsp60	33.3 %	.0%	20.0%	
	Total		**Count**	**3**	**2**	**5**	
			% within Hsp60	**100.0 %**	**100.0%**	**100.0%**	

Not known	Category	With ACS & Killip class	Count	3		3	
			% within Hsp60	100.0 %		100.0%	
	Total		**Count**	**3**		**3**	
			% within Hsp60	100.0 %		100.0%	

Obesity				**Hsp60**		**Total**	
				No	**Yes**		**P value**
No	Category	With ACS & Killip class	Count	2	3	5	0.500
			% within Hsp60	28.6%	42.9%	35.7%	
		Without ACS & killip class	Count	5	4	9	
			% within Hsp60	71.4%	57.1%	64.3%	
	Total		**Count**	**7**	**7**	**14**	
			% within Hsp60	**100.0%**	**100.0%**	**100.0%**	
Over weight	Category	With ACS & Killip class	Count	16	12	28	0.132
			% within Hsp60	53.3%	75.0%	60.9%	
		Without ACS & killip class	Count	14	4	18	
			% within Hsp60	46.7%	25.0%	39.1%	
	Total		**Count**	**30**	**16**	**46**	
			% within Hsp60	**100.0%**	**100.0%**	**100.0%**	

Tab.53

Age				Hsp60		Total	P value
				No	Yes		
18-45	Category	With ACS & Killip class	Count	4	4	8	0.134
			% within Hsp60	23.5%	57.1%	33.3%	
		Without ACS & killip class	Count	13	3	16	
			% within Hsp60	76.5%	42.9%	66.7%	
	Total		**Count**	**17**	**7**	**24**	
			% within Hsp60	**100.0%**	**100.0%**	**100.0%**	
46-80	Category	With ACS & Killip class	Count	14	11	25	0.609
			% within Hsp60	70.0%	68.8%	69.4%	
		Without ACS & killip class	Count	6	5	11	
			% within Hsp60	30.0%	31.2%	30.6%	
	Total		**Count**	**20**	**16**	**36**	
			% within Hsp60	**100.0%**	**100.0%**	**100.0%**	

Regression analysis for hsp 60 in cases alone :

Coming to HSP 60,none of the traditional risk factors seem to have any much influence in the cases .On regression analysis,the adjusted R square values for the HSP 60 is -0.201,with a significance of 0.818,which is not statistically significant.This indicates that HSP 60 is influenced upto 20% by the traditional risk factors in cases.

Model Summary[b]

Model	R	R Square	Adjusted R Square	Std. Error of the Estimate	Sig
1	.570[a]	.324	-.201	.55412	0.818

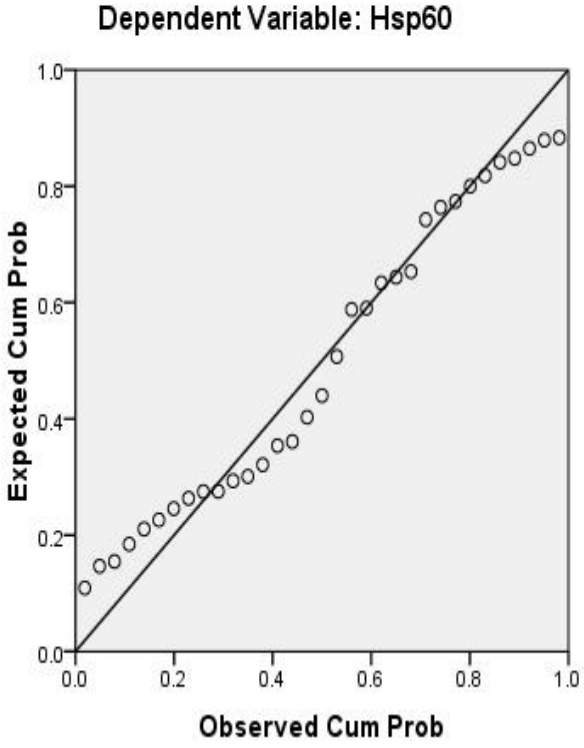
a. Predictors: (Constant), Killip class, Physical activity, Diet, age, ACS, Obesity, TD2M, Socio economic profile, Family History, SHTN, Stress, sex, Habits, Dyslipidemia

Coefficients[a] **Tab.54**

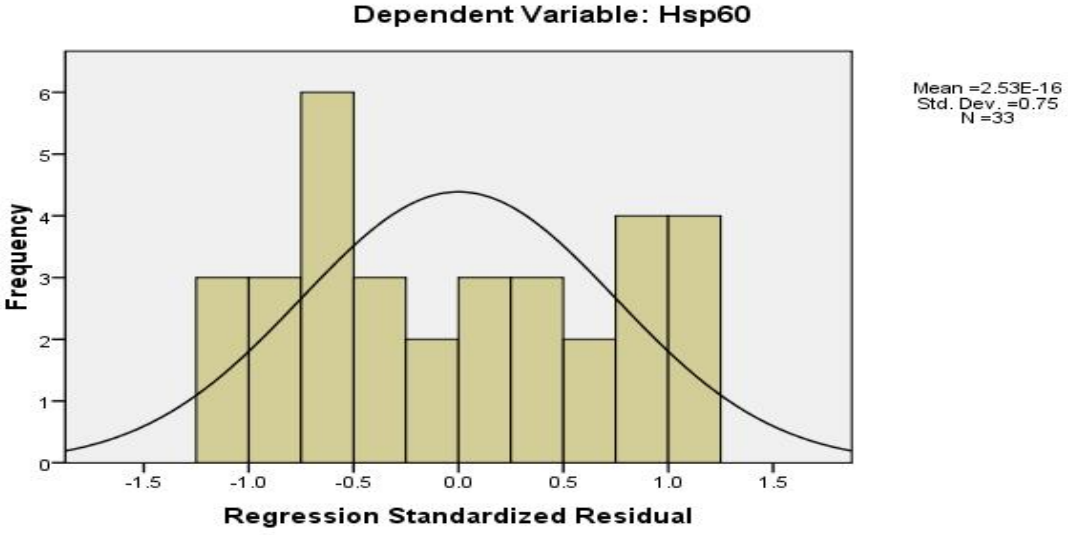
Model		Unstandardized Coefficients		Standardized Coefficients	T	Sig.
		B	Std. Error	Beta		
1	(Constant)	1.316	.916		1.437	.168
	Age	.171	.309	.147	.554	.587
	Sex	.160	.348	.131	.461	.651
	Socio economic profile	-.046	.120	-.097	-.385	.705
	Physical activity	-.244	.323	-.213	-.755	.460
	Diet	.127	.188	.183	.678	.506
	TD2M	-.221	.226	-.220	-.979	.340
	SHTN	-.010	.267	-.010	-.038	.970
	Dyslipidemia	-.644	.556	-.422	-1.159	.262
	Habits	.089	.111	.226	.805	.432
	Family History	-.309	.246	-.307	-1.260	.224
	Stress	.076	.153	.175	.500	.623
	Obesity	-.237	.169	-.326	-1.399	.179
	ACS	.007	.120	.017	.062	.951
	Killip class	.155	.196	.255	.791	.439

a. Dependent Variable: Hsp60

Normal P-P Plot of Regression Standardized Residual



Histogram



The analysis of other risk factors like gender, waist circumference and waist hip ratio due to limitation of data collection in stipulated time was not done. Waist hip ratio was not collected for the reason that most of the cases came with complication of acute coronary syndrome. These measurements were not collected at time of discharge in the cases who got successfully treated and discharged, as the admission waist and hip ratio differed from the discharge ones, due to loss of free fluid due to administration of diuretics in the patients who presented with volume overload and patient had some amount of weight loss during hospital stay due to diseases state and also due to low fat, low calorie diet.

In case of gender, as the samples had to be collected in a stipulated running time of the wells for HSP 60 in a duration of 60 days ,this parameter was not been analyzed in a statistically significant numbers. As the selection of cases never had inclusion of gender as priority. In our study we had total of 21.2% of females in both cases and 78.8% of males in cases .In controls, however,the ratio varied, with 40.7% being females and 59.3% being males. As the major aim of the study is to analyze level of infection and inflammation in acute coronary syndrome patients. We have not analyzed the data in the cases on the base of gender due to relatively low percentage of female population.

DISCUSSION

Heat shock protein 60 is a disease associated molecular pattern which is released under hemodynamic stress conditions from the mitochondria and cytoplasm of the vascular endothelial cells[56]. It has various levels of distribution in the cell, in endoplasmic reticulum, mitochondria, cell surface and cytoplasm[66]. HSP 60 belonging to the family of chaperonins, is a group of autoantigens based on the fact that it is a highly preserved molecule in eukaryotes and prokaryotes. Our study highlighted this molecular mimicry concept of HSP 60, where exposure to various bacterial and viral HSP 60 in a person's lifetime stimulates production of CD4 + T cells and antibodies against these molecules, which have the potential to act on human HSP 60 released under hemodynamic stress into circulation and initiate or accelerate inflammation in the vascular tree and precipitate major vascular events like acute coronary syndrome. It was found in a study by, M. Knoflach, S.Kiechl, M.Kind et al that in the initial phases of atherosclerotic process, CD4 + T cells are found in large numbers which mount reaction against HSP 60 and accelerate the process of atherosclerosis[67]. This count of CD4 + T cells is more in young population, hence the process of atherosclerosis mediated by HSP 60 can start in a very young age as evident by carotid intimal lesions. The analysis of ARMY study by M. Knoflach et al highlighted HSP 60 as one of the risk factor for atherosclerosis at a younger age[67].

In our study the levels of HSP 60 were found to be elevated in acute coronary syndrome patients as compared to controls with a significant ODDS ratio and confidence interval(CI). However the distribution of seropositivity of HSP 60 evaluated in our study had no statistically significant p value between case and controls. This indicates wide

spread of either infection associated or stress associated circulation of heat shock protein 60 in the body. Also suggests larger population evaluation of HSP 60 values.

The control arm in our study was healthy population with no evidence of coronary artery disease as per ECG. However the level of atherosclerosis in them as seen in other studies through carotid intimal thickening has not been evaluated due to financial constrains. The control arm had larger incidence of overweight population, which can act as hemodynamic stressor and can cause release of HSP 60 into circulation. The role of antibodies to HSP 60 has to be highlighted here, which are a more direct marker of atherosclerosis in human body[(66)].

Our study showed that subjects with inferior wall MI had elevated levels of HSP 60 compared to anterior wall MI and had more complications. These findings support the use of HSP 60 as a prognostic marker in future.

A study by Zang X et al, showed increased risk of CAD in patients with elevated HSP 60 levels and much more risk when patients had elevated antibodies to HSP 60 levels[(54)].

The value of HSP 60 as a prognostic marker was supported by a study in emergency department by , DH Birnie, LE Vickers et al where they found that patient visiting their hospital with chest pain had a poor prognosis on follow up a year later when they had elevated HSP 60 levels at admission[(68)].

In our study, the role of inflammation in acute coronary syndrome has been highlighted for the fact that our cases had statistically significant elevated levels of HSP 60, compared to control group. In our case control study, we evaluated the role of infection in causing acute coronary syndrome through activation of autoimmune pathways where, the level of infection in the body was measured indirectly by assessing

HSP 60 and the inflammatory pathway activation responsible for ACS by measuring circulating levels of HSP 60

Based on this concept, we highlighted the role of inflammation mediated activation of plaque rupture causing ACS. The role of infection in activating or progressing inflammation is evident in our study. As our cases who had complications (9 patients) and who had death during hospital stay (4 patients) had both elevated levels of hsCRP and HSP 60

Previous Studies:

A study by Biasucci LM et al, proved that unrelated to even hsCRP, elevated levels of Chlamydial HSP 60 was a marker for ACS which has both good sensitivity and specificity. In this study HSP 60 and hsCRP were evaluated in 179 patients with unstable angina and 40 patients with ACS against 30 control population[(56)].

A study by Zhang X et al in a group of 1003 CHD patients with controls found to have increased risk of CHD in subjects with elevated levels of HSP 60 and antibodies to HSP 60[(54)]. The risk for ACS was elevated when traditional risk factors were also taken into consideration in these subjects[(54)].

In our study we have proved that hsCRP is by itself an independent marker of the level of atherosclerosis in human body associated to an extent with complication secondary to ACS. hsCRP was significantly elevated in both our patients who had restenosis of drug eluting stent within a week of procedure. The elevation of hsCRP was independent of traditional risk factors. In our study, traditional risk factors like diabetes mellitus, hypertension, physical inactivity and others influenced only 23% of the levels of circulating hsCRP. Similarly even HSP 60 values were influenced a little by traditional

risk factors. This highlights the concept that irrespective of traditional risk factors causing inflammation, infection has a significant role in causing inflammation leading to ACS.

Our study does not deny the failure of previous antibiotic trials[47-49] where antibiotics were used to treat ACS. As the organisms like Chlamydia pneumonia were targeted in antibiotic trials (macrolide trials) where, the organism is not responsible for the ongoing inflammation, rather it is a one hit hypotheses

The organisms effect the vascular and cause ongoing inflammation even at clinically undetectable levels and once effected can cause ongoing proliferation of CD4 + T cells and cause inflammatory mediated atherosclerosis[66]. The activation of inflammatory pathways increases the levels of pro inflammatory cytokines like IL-1P, IL-12, IL-8, IL-18 other chemokines and interferon gamma can occur. On the other hand anti inflammatory cytokines also are activated like IL-10 and tumor growth factor beta[25]. The balance between these pro inflammatory and anti inflammatory markers decide levle of atherosclerosis in a human being.

From earlier studies it is evident that autoimmunity to heat shock protein especially HSP 60 exists even in normally healthy individuals, as this will be released into circulation under the influence of any stress factor on vascular structures[66]. This explains our findings of seropositivity of HSP 60 even in our controls, as they had traditional risk factors especially obesity was predominant in our population. It was evident from earlier studies that central obesity will cause vascular stress and increased inflammation, which explains the reason for prevalence of hsCRP elevation in our controls[19]. However, obesity was not statistically significant in influencing the presence of both hsCRP and HSP 60 in both cases and controls. Diabetes had a statistically significant role in influencing the levels of hsCRP in our cases[19].

Another major factor associated with difference in levels of HSP 60 can be genetic variability among cases. HSP 60 is presented to the CD4 + T cells through toll like receptor, when single nucleotide polymorphism related to these receptors are present, then HSP 60, even though patient is infected need not cause, inflammation[69,70]. The role of HSP 60 in activating β cells is yet to be established and requires further studies[66].

Our major area of interest in this study is to establish the importance of inflammation in atherosclerosis, which can be mediated through infection, as India has rampant incidence of various infectious diseases.

Through this study we spotlight the importance of treatment modalities focusing on inflammatory pathways in ACS.

The role of HSP vaccines, that cause tolerance to pathogenesis mediated through HSP is established in phase I and II trials to treat melanomas (metastatic). Similar principle can be used and animal studies examples can be utilized where vaccines against HSP caused increased levels of protective cytokines levels like IL-10 and decreased the plaque burden in the treated animals, for the treatment of human atherosclerosis mediated diseases like acute coronary syndrome.[68]

One major limitation of these values and relation between infection and atherogenesis is time. As infection exposure occurs at infancy and childhood, but the clinical manifestations are mostly evident in adult stage.[70] It is the massive vascular involvement or is it burden of pathogens or is it inflammation or existence of risk factors, which is responsible for adult manifestation of atherosclerosis has to be further evaluated. This explains the role of traditional risk factors like oxidative stress, inflammation, infection and lipoprotein a, in causing complex mechanism in atherogenesis and cardiovascular diseases.

LIMITATIONS:

1. Role of HSP 60 as marker of chronic infection requires further analysis in larger group to evaluate for the difference between significant ODDS ratio and statistically insignificant p value
2. Assessment of waist hip ratio in all the cases could not be done. This remains a major limitation as in Indian population central obesity is one major cause for inflammatory process in body
3. Few patients expired within few hours of admission ,for them stress scales could not be evaluated
4. For all patients admitted coronary angiogram was not done to know the exact coronary lesion
5. Few patients have been thrombolysed outside and for such patients samples have been taken after thrombolyses which might affect levels of hsCRP.

SUGGESTIONS:

1. From the analysis of obtained data from our study we suggest further requirement of analysis of role of infection in atherosclerosis process.This involves study of various other molecules like IL-7,other heat shock proteins like HSP 70,HSP 65 and others.
2. Genetic variations or single nucleotide polymorphisms related to HSP60 as polymorphisms of toll like receptors or IL-1 beta receptors can be analysed to know the variation in HSP 60 levels in our population.
3. Targeted therapy involving immunisation against HSP 60 may decrease atherosclerosis process as suggested by animal studies,hence this treatment modality can be tried in humans too.
4. Larger population of STEMI cases has to be studied to know the variation of role of infection and inflammation in various coronary artery lesions in a statistically significant manner.
5. Potential involvement of infection as a novel risk factor in cases of young MI can be evaluated based on these observations.This can partly explain the fact why India is witnessing a higher incidence of young MI in recent days as India has larger incidence of infectious diseases compared to developed nations.
6. Inflammation role in acute coronary syndrome can further be studied with cytokines levels which are early markers of inflammation (IL-1,IL-6).
7. Further role of pathological and biochemical analysis of thrombus may give us a better idea of level of inflammation and cholesterol content in the plaque which can help us to tailor treatment to each individual.

FUTURE PROSPECTIVES:

In future, genetic studies can be done on inflammation as we succeeded in achieving the positive relation between hs CRP and ACS .The CANTOS trial (The CANAKINUMAB Anti inflammatory Thrombosis Outcomes Study) is designed to test the hypotheses that IL-1beta inhibition will reduce major cardiovascular events in persons with pre existing CAD.This is the first true test to support our hypothesis that interrupting on inflammatory pathway involved in atherosclerosis will reduce cardiovascular events.62.The Darapladib trial too proved the fact that anti-inflammatory drugs reduce the atherosclerotic plaque burden.[61].

CONCLUSION:

It was proved through our study that elevated levels of HSP 60 has a role in acute coronary syndrome and it can be used as a prognostic marker to know the outcome of the patient especially when clubbed with hsCRP levels. However statistical significance of HSP 60 as a potential risk factor in acute coronary syndrome requires studies in all clinical spectra of acute coronary syndrome. Role of inflammation was again proved in our study with statistically significant levels of hsCRP in STEMI patients irrespective of traditional risk factors. Hence role of genetics in relation to inflammation has to be evaluated further to know how inflammatory response varies from individual to individual.

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LIST OF TABLES

LIST OF FIGURES

GLOSSARY

ACS – acute coronary syndrome

AWMI – anterior wall myocardial infarction

AW+LWMI – anterior wall and lateral wall myocardial infarction

CAD- coronary artery disease

CAG – coronary angiogram

ECG- electrocardiogram

HTN- hypertension

HSP- heat shock protein

HSP 60 heat shock protein 60

hsCRP – high sensitivity C reactive protein

IWMI – inferior wall myocardial infarction

IWMI +PWMI – inferior and posterior wall myocardial infarction

MI – myocardial infarction

PCI – percutaneous coronary intervention

PWMI – posterior wall myocardial infarction

RDA – recommended dietary allowance

STEMI – st elevation myocardial infarction

T2DM – type 2 diabetes mellitus

		0- 18-45 yrs	0-MALE	0-NO	0-NO	I	1-INACTIVE				0-NO		0-NO	0-NO	1-AWMI	1-CLASS I		0-NO	0-NO LVD	0-NO RWMA	0-NOT DONE	0-NO LESION		0-AMA			0-NOT DONE
		1-46-80yrs	1-FEMALE	1-YES	1-YES	II	2-MINIMALLY ACTIVE		0-NO	0-NO	0-NO	1-SMOKER	0- NO	1-MILD	1-OVER WEIGHT	2-AW+LWMI	2-CLASS II		1-YES	1-MILD LVD	1-LAD	1-MEDICAL	1-SVD	1-LAD	1-DEATH	0-NO		1-OUTSIDE
				ELEVATED	ELEVATED	III	3-HEPA ACTIVITY	0-As per RDA	1-YES	1-YES	1-YES	2-ALCHOL	1- YES	2-MODERATE	2 - OBESE	3-IWMI	3-CLASS III			2-MODERATE LVD	2-RCA	2-CABG	2-DVD	2-LCX	2-DISCHARGED	1-YES		2-INHOSPITAL
				>0.5MG/DL	>2NG/ML	IV		1-More than RDA			2-NOT KNOWN	3-BOTH		3-SEVERE		4-PWMI	4-CLASS IV			3-SEVERE LVD	3-LCX+RCA/	3/3*-PRIMARY/ELECTIVE*	3-TVD	3-RCA	3-DISCHARGED	2-CHRONIC		3/3*-STREPTOKINASE/ALTEPLASE
						V		2-Less than RDA								5-IW+PWMI				4-LVDD	4-LAD+RCA	PTCA			AT REQUEST			4/4*-FAILED/COMPLICATIONS*

S No.	Patient Name	Age	Sex	HSCRP	HSP 60	SOCIO ECO	PHYSICAL ACTIVITY	Diet	T2DM	SHTN	Dyslipidemia	Habits	Family History	Stress	Obesity	ACS	Killip Class	PRESENTING BP	PRESENTING PR	COMPLICATIONS	ECHO	ECHO	CAG	CAG	CAG	OUTCOME	INFECTION	OTHERS	THROMBOLYSIS	
1	Meenashi		1	1	0	1	II	1	0	0	1	1	0	0	2	2	1	1	140/90	96	0	1	1	2	3	1,2,3	2	0		0
2	Puspharaj		1	0	1	0	III	1	2	1	0	1	1	1	2	1	1	1	150/80	76	0	4	1	1	3	1,2,3	2	0	CIN	0
3	Mani		1	0	1	1	III	1	2	1	1	1	3	1	1	0	1	3	160/100	77	0	2	1	3*		1	1	2	0	Mild Renal Failure	4
4	Manickam		1	1	1	1	IV	1	1	0	0	1	0	1	2	1	3	2	130/90	74	1	-MR		2	2	0	0	0	0	0	0
5	Subramaniam		1	0	1	1	II	1	1	1	1	2	3	0	2	1	3	4	NOT RECORDABLE	NOT FELT	1-CARDIAC ARREST		3		0	0	0	1	1	CPR	0
6	Ganesan		1	0	0	0	II	2	1	0	1	1	3	1	1	2	1	2	120/100	64	0	1	1	3*		1	1	2	0		2,3	
7	Kandasamy		0	0	0	1	IV	2	1	0	0	1	3	0	2	1	1	3	100/80	100	1	-ISCHEMIC VT/VF		1	1	1	0	-RECANALISED	1	2	0		2,3	
8	Nagaraj.P		0	0	0	1	I	2	0	0	0	1	1	0	0	0	1	1	90/60	68			1	1	3	1	1	2	0		0
9	Suppathal		1	1	0	0	I	0	0	0	1	1	0	1	1	2	3	1	130/80	74			0	0	0			2	0	ANEMIA,HYPOTHYROIDISM		0
10	Ganesh.T		1	0	0	0	II	2	1	0	0	1	3	0	0	1	1	1	120/70	68			4	0	1	0	-RECANALISED	1	2	0	CAD		0
11	Palanisamy.N		1	0	1	1	I	1	1	0	1	1	1	0	0	2	1	2	100/80	81			2	4	3*		2	1,2	2	0		2,3	
12	Natchammal		1	1	1	1	I	1	0	0	0	1	0	0	1	0	5	2	90/50	56	2:1 BLOCK,CHB					3	2	1,3	1	0			0
13	Selvam		0	0	1	1	II	1	0	0	0	1	0	0	1	1	3	1	80/60	65			1	2		0			2	0			0
14	Dhandapani		1	0	0	0	III	1	1	1	1	1	0	1	1	2	1	1	100/70	84			2	1		3	1	1	2	0			0
15	Chandrasekhar		0	0	1	0	II	1	0	1	0	1	3	0	1	2	1	2	130/70	92	POST THROMBOLYTIC BLEED		1	1		3	1	1	2	0		1,3*	
16	Kumarasamy.R		1	0	0	0	II	2	1	1	0	1	1	0	0	1	3	1	100/60	98			2	3	3*		3	1,2,3	2	0	IHD,LEFT UL GRANULOMA BENIGN		2
17	Ravi.M		0	0	0	0	I	1	2	1	0	1	0	0	3	2	1	1	120/90	96			1	1		3	1	1	2	0			0
18	Chandran.B		0	0	1	1	II	1	2	1	1	1	3	0	2	1	3	2	110/70	124	VT/CHB SECOND TIME		2	2		3	3	1,2,3	2	0	CAD		2
19	Salaudeen		1	0	1	1	III	1	1	1	1	1	1	0	1	1	1	1	110/70	96			3	1	2	3	1,2,3		2	0	BRONCHIAL ASTHMA,SARIDON AL		0
20	Solomon.A		0	0	0	0	II	1	2	0	0	1	0	0	2	1	3	1	120/70	76			1	2	0				2	0			0
21	Jacob Augustine		1	0	0	1	I	1	1	0	0	1	2	0	2	2	4	2	70/50	162			1	2	1	3	1,2,3		2	0	CAD		0
22	Ramesh Kumar		0	0	0	0	III	1	0	0	1	2	3	1	NOT AVAILABLE	1	1	4	130/90	68	CARDIOGENIC SHOCK								0	0	CARDIAC SHOCK,INTUBATED		
23	Gnanpoo		1	1	1	0	IV	1	0	1	0	2	0	0	NOT AVAILABLE	0	1	2	80/40	95			2	1					0	0			
24	Joseph Chandran		1	0	1	1	I	1	2	1	0	1	0	1	3	1	1	1	140/90	80			1	1	1	1	1		2	0	BRONCHIAL ASTHMA	2,3	
25	Ganapathy		1	0	1	0	II	2	0	1	1	1	1	0	0	1	2	2	90/50	100	MR,PAROXYSMAL AF		2	3					2	1	HCAP		0
26	Subramaniam*		1	0	1	1	IV	1	1	1	1	1	3	1	3	2	1	2	100/50	98	MR		2	1	2	3	1,2,3		1	1,2	HEPATITIS B,SEPSIS	1,3	
27	Subbappa		1	0	0	0	I	1	1	1	1	1	3	1	1	1	1	2	110/80	91	MR		2	2	1	3	1,2,3		2	0	D2 TOTAL OCCLUSION-POBA DONE		0
28	Vellingiri.P		1	0	1	0	IV	1	1	1	1	1	0	0	3	2	1	2	150/100	135			1	1					3	0			0
29	Sennimalai Gounder		1	0	0	0	II	1	0	1	1	2	1	1	NOT AVAILABLE	1	1	2		VT ,REVERTED			1	1					1	0			0
30	Thimmasamy		1	0	1	0	IV	1	0	0	1	1	1	1	2	0	1	1	110/60	92			1	1	3*		2	1,2	2	1	lower respiratory infection	1,3*	
31	Valliammal		1	1	1	0	II	1	0	1	1	1	0	0	2	2	3	2	130/80	48	MR		2	2	1	3	1,2,3		2	0	MENINGIOMA		0
32	Krishnasamy.T		1	0	1	0	I	1	1	1	0	1	0	1	1	2	3	2	100/50	100			1	2					2	0	MILD RF/RT CONTRACTED KIDNEY	2,3	
33	Rajendiran.A		1	1	0	1	II	1	1	1	0	1	2	1	2	1	3	1	130/100	79	MR,MVP-PML		4	1	1	1	1		0	0	SUBCLINICAL HYPOTHYROIDISM		0
				18	15	0	38	27	19	17	37	42	14	44	40	61	58	0	2713	0	54										

	0-18-45yrs	0-Male			I->5571	1-INACTIVE							0-NO				
	1-46-80yrs	1-Female	0-NO	0-NO	II	2-MINIMALLY ACTIVE	0-AS PER RDA				0-NO	0-NO	1-MILD	0-NO		0-NO	
			1-YES	1-YES	III	3-HEPA ACTIVE	1-MORE THAN RDA	0-NO	0-NO	0-NO	1-SMOKER	1-YES	2-MODERATE	1-OVERWEIGHT		1-YES	
					IV		2- LESS THAN RDA	1-YES	1-YES	1-YES	2-ALCHOLIC		3-SEVERE	2-OBESITY			
					V - < 836						3-BOTH						

S I	Patient Name	Age	Sex		HSCRP	HSP60	SOCIOECO	PHYSICAL ACTIVITY	DIET	T2DM	SHTN	DYSLIPIDEMIA	Habits	Fam his	Stress	Obesity	Others	RECENT INFECTION	
1	Bhavani MR		1	1	Y	N	I		1	2	0	0	1	0	1	0	1 Asthmatic		0
2	Sundarambal		0	1	N	Y	III		1	0	0	0	1	0	0	1	0 Occasional pain killer		1
3	Mani.P		1	0	Y	Y	III		1	1	0	0	1	0	0	1	1		0
4	Soundarajan.P		1	0	N	N	I		1	1	1	0	1	0	1	0	1 ? Skin Allergy		0
5	Sundaram.M		1	0	N	Y	I		1	0	0	1	1	1	0	0	1 Not on anti htn drugs		0
6	Gurusamy.K		0	0	N	N	II		1	1	0	0	1	3	0	0	1 Renal calculi		0
7	Chinnasamy		0	1	N	N	II		1	0	0	0	1	0	0	1	0		0
8	Soby.C.I		0	0	N	N	I		1	1	0	0	1	2	0	1	1		0
9	Praveen Chakrav		0	0	N	N	II		1	0	0	0	0	0	0	3	0		0
#	Velayudham K		0	0	N	N	I		2	0	0	0	1	2	0	0	0		0
#	Subramaniam		1	0	N	Y	II		1	1	1	0	1	2	0	1	1		1
#	Senthilkumar.P		0	0	Y	N	II		1	1	1	1	1	2	0	1	1 Not on drugs for HTN/T2DM		0
#	Sarasvathi.T		1	1	N	N	I		1	0	0	0	1	0	1	1	0		0
#	Hemanthkumar.R		0	0	N	N	I		1	0	0	0	1	0	0	2	2		0
#	Umarani		1	1	Y	Y	I		2	0	1	0	1	0	0	1	1		0
#	Subbulakshmi		0	1	N	N	IV		3	2	0	0	1	0	0	0	0		0
#	Sumathi.G		0	1	N	N	I		2	1	1	0	1	0	0	1	1 On Siddha medication		0
#	Sivasamy.T		1	0	N	N	II		1	0	0	0	1	0	0	0	1		0
#	Samuel Mani.P		1	0	N	N	I		1	1	0	0	1	2	0	0	2		0
#	Sujin.R		0	0	N	N	I		1	1	0	0	1	0	0	1	1 Childhood Tb-treated		0
#	Harikrishnan.M		0	0	N	Y	I		1	0	0	0	1	0	0	0	0		0
#	Amit Kumar		0	0	N	N	I		2	0	0	0	0	3	0	2	1 H/O Hyperthyroidism		0
#	Amutha.H		0	1	Y	Y	I		1	1	0	0	0	0	0	1	0 RA,ON STEROIDS AND DMARDS		0
#	Ranganayagam.G		1	1	N	Y	III		1	2	0	0	1	0	0	0	0		0
#	Murugesan.N		1	0	Y	N	II		2	0	0	0	1	1	1	1	1		0
#	Selvi		0	1	Y	N	I		1	2	0	0	0	0	1	0	1		0
#	Padmavathi		0	1	N	N	I		1	1	0	0	1	0	1	0	1		0